AD_____

Award Number: DAMD17-00-1-0033

TITLE: Locating a prostate cancer susceptibility gene on the X chromosome by linkage disequilibrium mapping using three founder populations in Quebec and Switzerland

PRINCIPAL INVESTIGATOR: Dr. William Foulkes

CONTRACTING ORGANIZATION: Montreal General Hospital Institute
McGill University
Montreal (Quebec) Canada H3A 2T5

REPORT DATE: September 2006

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-09-2006	Final	01 Mar 00 – 30 Aug 06

4. TITLE AND SUBTITLE
Locating a prostate cancer susceptibility gene on the X chromosome by linkage disequilibrium mapping using three founder populations in Quebec and Switzerland

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-00-1-0033

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. William Foulkes

E-Mail: william.foulkes@mcgill.ca

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Montreal General Hospital Institute
McGill University
Montreal (Quebec) Canada H3A 2T5

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

At the Montreal site, 240 participants (195 cases) have consented to participate and 230 participants (185 cases) had their blood drawn. The pedigrees for cases and some controls have been drawn. Ishihara charts were shown to all cases and controls and the results were recorded. At the Switzerland site, case ascertainment is complete and 250 patients have been contacted; 185 have had a consultation with a DNA sampling. As the X chromosome gene has proved to be elusive, we have focused our attention on candidate genes and have studies CHEK2, PALB2, BRCA1, BRCA2 as well as other candidate genes in this series of cases. We have identified several novel mutations in CHEK2 and PALB2, but none of these mutations appear to be thus far associated with prostate cancer risk. Other known mutations, such as BRCA1: 187delAG and BRCA2: 6174delT do not appear to be more frequent in men with prostate cancer. Our work did not support the initial suggestion that some Ashkenazi Jewish men with prostate cancer carried a prostate cancer-associated allele on chromosome 7q. Prostate cancer genetics remains a difficult area of research; our work has mainly eliminated various candidate genes rather than identify causative mutations in prostate cancer susceptibility genes.

15. SUBJECT TERMS
None provided.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	87	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

Task 1: Case ascertainment, contact, consent, interview, DNA extraction and pathology confirmation.

- Obtain approval for this study from relevant IRBs.

  As discussed in our previous report, we did not pursue ethical approval at the Chicoutimi site and limited ethics approval to McGill University Hospital sites and Sion and affiliated hospitals and clinics, Le Valais, Switzerland.

- Identify all prevalent cases of prostate cancer at hospitals serving the three populations under study: Chicoutimi, McGill University Hospitals (Quebec) and Sion and affiliated regional hospitals, Valais, Switzerland. This will be carried out by contacting medical records, out-patient charts and cancer registries, confirming that the patient is living and then seeking permission from treating physicians (who are collaborators on this proposal) to contact their patients by letter.

  Montreal: This goal was achieved at the McGill University Hospitals last year and has been on-going this year. One hundred and eighty-five cases were ascertained in total.

  Valais: The head of the *Registre Valaisan des Tumeurs* has established a list of all patients diagnosed with prostate cancer since 1997 and who are residents in the *canton du Valais* (n = 730). Only patients whose surnames indicate an origin from the *canton du Valais* (based on the data from the *Association Valaisanne d'Etude Généalogique*) were conserved and thus considered as eligible for the study (n = 558). At the end of February 2004, a mailing was sent to the private physicians in charge of the living patients. We proposed that they send an information sheet about the research project to their patients with the phone number of the research nurse to be contacted. This mode of recruitment turned to be not efficient (<40 patients recruited).

- Identify incident cases through urology clinics at the three centres (Chicoutimi, McGill University, Sion). Method of contact as for prevalent cases: also, eligible individuals will be approached directly in the clinic.

  Montreal: This goal has been achieved at the Montreal site. McGill Urology Associates are helping to identify new cases of prostate cancer.

  Chicoutimi: As stated above, we have abandoned our efforts at this site.

  Valais: With the collaboration of the Service of Radio-oncology at the Hospital of Sion, the Institute of pathology of the *Institut Central des Hôpitaux Valaisans* and 5 urologists in private practice in the canton du Valais, a series of prevalent cases eligible for this research study were recruited.

- Contact relatives via case

  Montreal: 42 controls have been recruited into the study at this site
  Valais: There have been no controls recruited to date at this site (see below)

- Consent all eligible participants (case n~640)

  Montreal: A total of 195 patients at the McGill University Hospital sites have given their consent to participate. We have DNA from 185 men. We have appointments to meet another 15 men that wish to participate in this study over the next few months. We have purchased DNA from Ashkenazi Jewish controls from Israel, as recruitment of controls was very slow in Montreal. A total of 18 affected men have refused to participate and we have found 7 of the ascertained are deceased.

  Valais: A total of 190 patients at the Sion Hospital site have given their consent to participate. 1 person was excluded. So far, 185 DNA samples have been collected. The Sion research team has found getting access to familial controls quite difficult and, in agreement with the PI, Dr William Foulkes, the Sion team has started to collect non-familial age- and ethnically-matched male controls from the blood donors' clinic in the Hospital of Sion and from a local familial medicine clinic. Currently, we have DNA from 51 controls and we expect to collect 140 DNA samples in the next 2 months, to reach a total of at least 190 controls.

- Interview and construct three-generation pedigree for each case and control

  Montreal: A total of 195 pedigrees have been drawn for cases for McGill University Hospital site since the commencement of the study. We have also drawn 42 pedigrees for the controls that have participated in the study.
  Valais: A total of 185 pedigrees have been drawn for cases at the Sion site.

- Show Ishihara charts to cases

  Ishihara charts have been shown to all participants and controls at all sites where the study is being conducted (McGill and Valais).

- Draw blood from all consenting participants

  Blood has been drawn from >95% of participants that have been consented at all sites (Montreal and Valais)

- Extract DNA locally at each participating centre, transfer aliquots of DNA to PI laboratory for quality check and storage

  DNA has been extracted at the McGill University Hospital and the Switzerland

site. An aliquot of DNA from the Sion site will be transferred to the PI laboratory.

- Transfer representative slides and blocks to Montreal for central pathology review

  Slides and blocks from patients ascertained at the McGill University Hospital site have been transferred to a central pathologist for his review. The pathologist has completed his review of the material from 178 of the participating patients. We now have a standard Gleason Score for all cases where we have been able to locate a pathology block. Cases at the Sion site will be reviewed both in Switzerland and in Montreal

- Create central database at the Montreal General Hospital Research Institute

  We have developed a database at the McGill University Hospital sites and it is continually updated as more cases and controls are recruited.

Tasks 2 and 3: Genotyping of DNA from cases and controls, followed by statistical analysis

Specific Aims for this reporting period:

1. To study *CHEK2* and its contribution to prostate cancer in the AJ population.
2. To study the recently identified breast cancer susceptibility gene PALB2 in selected familial cases of prostate cancer.

Studies and Results:

Project 1: *CHEK2* in the Ashkenazi Jewish Population

To investigate whether *CHEK2* plays an important role in the development of prostate cancer (PRCA) in the Ashkenazi Jewish (AJ) population, we re-sequenced all exons and intron-exon boundaries of *CHEK2* in 75 AJ individuals with prostate, breast or no cancer (n = 25 each). We identified seven coding SNPs (five are novel) that changed the amino acid sequence, resulting in R3W, E394F, Y424H, S428F, D438Y, P509S and P509L. We determined their frequency in probands from 76 AJ families collected by members of the International Consortium for Prostate Cancer Genetics (ICPCG) where ≥ 2 men were affected by PRCA and ≥ 1 affected man provided a DNA sample. Only one variant, Y424H was identified in more than two families with an affected proband. Exon 11 was screened in nine additional families for a total of 85 families with at least one affected genotyped. The Y424H variant occurred in nine affected cases from four different families. In one family, all three affected cases had the variant. In another, four of the five affected cases carried the Y424H variant. For the other two families, only one affected case out of two or three had this variant. Bioinformatic analysis showed that Y424H is a radical missense substitution that falls at a position that is invariant in vertebrate *CHEK2* orthologs. Both SIFT and

Align/GV-GD predict that this is a loss of function mutation. However, Y424H frequency was 8/702 in prevalent cases and 5/545 in controls (OR 1.23, 95%CI: 0.35-4.82, P =.79). Functional studies suggested that Y424H behaves like wt CHEK2. These results suggest that while the Y424H variant may have a subtle influence on PRCA risk, *CHEK2* has a minor overall role in PRCA susceptibility in the AJ population.

Project 2: PALB2 and prostate cancer

PALB2 (**P**artner **A**nd **L**ocaliser of **B**RCA**2**) is a new breast cancer susceptibility gene. Because BRCA2 is also a prostate cancer susceptibility gene, we screened 35 prostate cancer cases (14 Ashkenazi Jewish (AJ) and 21 French Canadian (FC) males) who had a family history of cancer defined as two or more affected cases and that were previously screened for the AJ or FC *BRCA1/BRCA2* founder mutations as well as *CHEK2:1100delC* and were found not to carry these mutations. We also analysed breast cancer cases at the same time. One mutation was found in a family without prostate cancer, but no clearly pathogenic mutations were identified in any of the other 67 strong family history breast cancer probands sequenced (average BRCAPRO score 0.58), in the FC moderate family history series or in the familial prostate cancer cases. A number of *PALB2* sequence variants were identified, all of which have been previously reported. The variant frequencies were similar to those already reported and common variants (frequency greater than 1%) such as Q559R, E672Q, G998E and T1100T were present in all three groups tested, with the exception of L337S, which was not seen in the FC population. These data reduce the likelihood that a significant fraction of non-*BRCA1/BRCA2* familial breast/ovarian/prostate cancer in the AJ and FC populations is due to common founder mutations in *PALB2*.

Significance:

Identification of variants in candidate genes in founder populations is an important step for validating their candidacy as prostate cancer susceptibility genes.

Task 4: Manuscript preparation

- Report major findings (2005-2006)

Published papers:

Full papers

1. Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR, Meyers DA, Eeles RA, Easton DF, Foulkes WD, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Bishop T, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Hsieh CL, Halpern J, Balise RN, Oakley-Girvan I, Whittemore AS, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Thibodeau SN, McDonnell SK, Cunningham JM, Zarfas KE, Hebbring S,Schaid DJ, Friedrichsen DM, Deutsch K, Kolb S,

Badzioch M, Jarvik GP, Janer M, Hood L, Ostrander EA, Stanford JL, Lange EM, Beebe-Dimmer JL, Mohai CE, Cooney KA, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela TLj, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson BA, Gronberg H, Camp NJ, Farnham J, Cannon-Albright LA, Seminara D; ACTANE Consortium. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. *Am J Hum Genet* 77(2):219-29, 2005.

2. Schaid DJ, McDonnell SK, Zarfas KE, Cunningham JM, Hebbring S, Thibodeau SN, Eeles RA, Easton DF, Foulkes WD, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Badzioch M, Bishop DT, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Guy M, Hsieh C-L, Halpern J, Balise RR, Oakley-Girvan I, Whittemore AS, Xu J, Dimitrov L, Chang B-L, Adams TS, Turner AR, Meyers DA, Friedrichsen DM, Deutsch K, Kolb S, Janer M, Hood L, Ostrander EA, Stanford JL, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Lange EM, Ho LA, Beebe-Dimmer JL, Wood DP, Cooney KA, Seminara D, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela T LJ, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson B-A, Grönberg H, Camp NJ, Farnham J, Cannon-Albright LA, Catalona WJ, Suarez BK, Roehl KA. Pooled genome linkage scan of aggressive prostate cancer: results from the International Consortium for Prostate Cancer Genetics. *Human Genetics* 120(4):471-85, 2006.

3. Tischkowitz MD, Xia B, Sabbaghian N, Reis-Filho JS, Hamel N, Li G, van Beers E, Li1 L, Khalil T, Quenneville L, Omeroglu A, Poll A, Lepage P, Wong N, Nederlof PM, Ashworth A, Tonin PN, Narod SA, Livingston DM, Foulkes WD. Analysis of PALB2/FANCN–associated breast cancer families. To be submitted February 2007.

4. Tischkowitz MD, Chen LQ, Friedrichsen-Karyadi DM, Kirchhoff T, Hamel N, Tavtigian SV, Kolb S, Nelson PS, Hood L, Narod SA, White KA, Ostrander EA, Isaacs WB, Offit K, Cooney KA, Stanford JL, Foulkes WD. Identification and characterization of novel SNPs in CHEK2 in Ashkenazi Jewish men with prostate cancer. To be submitted March 2007

CURRICULUM VITAE

WILLIAM DAVID FOULKES

BIRTHPLACE Penarth, Wales, UK.

ADDRESS BUSINESS

Division of Medical Genetics

Montreal General Hospital
1650 Cedar Avenue, Room L10-116
Montreal, Quebec, H3G 1A4
Tel: (514) 934-1934, local 44121
Fax: (514) 934 8273
Lab: (514) 937-6011, local 44201

Department of Medical Genetics
Cancer Prevention Centre
Sir M.B. Davis-Jewish General Hospital
3755 Cote Ste Catherine, Room C-107.1
Montreal, Quebec, H3T 1E2
Tel: (514) 340 8222, local 3851
Fax: (514) 340 8222, pause 2116/
(514) 340 8600Lab: (514) 340-8222, local 3361
Email: william.foulkes@mcgill.ca

HOME

45 Elmwood
Senneville, Quebec
H9X 1T6
Tel: (514) 457-6669

CITIZENSHIP Canadian, British

EDUCATION & TRAINING

1980	B.Sc. - Upper second class honours, Anatomy University of London
1984	MB.BS University of London
1984 -1985	House officer in Medicine and Surgery, Hackney and St. Bartholomew's Hospital, London
1985-1986	Senior House Officer Emergency Medicine, Whittington Hospital, London
1986 - 1987	Rotating Senior House Officer Department of Medicine St. Mary's and St. Charles Hospitals, London
1987 - 1988	Senior House Officer Departments of Medicine and Radiotherapy Royal Marsden Hospital, London
1988 - 1989	Registrar in General and Respiratory Medicine Ealing Hospital, Middlesex
1989 - 1990	Registrar in Gastroenterology Hammersmith Hospital, London
1990 – 1994	Ph.D. *A molecular genetic analysis of ovarian cancer* Completed as an external student of the University of London, at the Imperial Cancer Research Fund (Internal: Galton Laboratory, UCL)

FELLOWSHIPS

1990 - 1994	Clinical Research Fellow Human Immunogenetics Laboratory Imperial Cancer Research Fund London and Honorary Research Fellow, Family Cancer Clinic - St. Mark's Hospital,

London

(affiliated with the Division of Medical and Molecular Genetics, KGT Medical School, University of London)

APPOINTMENTS

1994 -	Medical Scientist, Montreal General Hospital
1996- 2002	Assistant Professor, Department of Medicine, McGill University, Montreal.
1996-2002	Assistant Professor, Department of Human Genetics, McGill University, Montreal
1996-	Senior Research Associate, Epidemiology Research Centre, Pavillon Hotel Dieu, Centre Hospitalier Université de Montréal (CHUM).
1996-	Project Director, Lady Davis Institute, Sir Mortimer B. Davis-Jewish General Hospital, Montreal
1996-	Assistant Physician, Montreal General Hospital
1996-	Assistant Physician, Royal Victoria Hospital, Montreal
1996-	Assistant Physician, Sir Mortimer B. Davis-Jewish General Hospital, Montreal
1998-2002	Assistant Professor, Department of Oncology, McGill University, Montreal
2001-	Principal Investigator, Canadian Genetic Diseases Network
2001-	Director, Program in Cancer Genetics, Departments of Oncology and Human Genetics, McGill University
2001-	Vice-Chair, Genetic VRC, Canadian Cancer Etiology Research Network
2002-	Associate Professor (tenure), Departments of Medicine, Human Genetics and Oncology, McGill University, Montreal

AWARDS RECEIVED

1979: Junior Scholarship in Anatomy, Physiology and Biochemistry, St Bartholomew's Hospital.

1983: Health Education Council Elective Scholarship "Diabetes in China".

1990-1994: Clinical Research Fellow Bursary, Imperial Cancer Research Fund, London.

1994-1997: Fast Foundation Award of the Montreal General Hospital Research Institute.

1997-1999: Fonds de la recherche en Santé du Québec: Chercheur-boursier clinicien. Junior 1

1997-2000: 175th Anniversary Bursary, Montreal General Hospital Research Institute.

1999-2002: Fonds de la recherche en Santé du Québec: Chercheur-boursier clinicien. Junior 2

2002-2007 : Fonds de la recherche en Santé du Québec: Chercheur-boursier clinicien. Senior

2003-2008: William Dawson Scholar, McGill University (equivalent Canada Research Chair, tier 2)

CURRENT COMPETITIVE GRANTS

Principal Investigator
Principal applicant: Foulkes, WD
CBCRA-IDEA: *BRCA1* splice variants and breast cancer risk: novel approaches using nanobiology.
($ one year, 2006-2007)

Principal applicant: Foulkes, WD
Co-investigators: Bismar, T; Aloyz, R; Ghadirian, P
CBCRA: Toward the biological treatment of BRCA1-related breast cancer: EGF, EGFR and tyrosine kinase inhibitors
($ over 3 years, 2006-2009)

Principal applicant: Foulkes, WD
Co-investigators: Nielsen, T; Mai, S
CBCRA: BRCA1, CDC4, Cyclin E, and chromsomal instability in breast cancer
($ over 3 years, 2005-2008)

Co-investigator
Principal applicant: Mai, S
Co-investigators: Foulkes, WD; Watson, P
Susan G Komen Breast Cancer Foundation
The three-dimensional telomeric signature(s) of DCIS
(US $ over three years 2006-2009)

Principal applicant: Isaacs, W
Co-applicants: Foulkes, WD; Epstein, J; Partin, A; Easton, D; Eeles, R; Maehle, L; Giles, G; Hopper, J; Whittemore, AS; Halpern, J; Hsieh, CL; Cussenot, O; Cancel, G; Jarvik, G; Bdzioch, M; Stanford, J; Ostrander, E; Schaid, D; Thibodeau, S; Gronberg, H; Cooney, K; Lange, E; Schleutker, J; Vogel, W; Cannon-Albright, L; Camp, N; Jianfeng Xu, Meyers, D.
NIH (USA): *Prostate cancer susceptibility: the ICPCG study.*
($ as personal award over 4 years, 2002-2006)

Principal applicant: Batista, R
Co-applicants: Foulkes, WD; Blancquaert, I; Cleret de Langavant, G; Gaudet, D; Godard, B; Laflamme, N; Marcoux, A; Rousseau, F
CIHR: *Programme de recherche en appui aux politiques de santé en génétique dans un souci de qualité, d'effcience et de bien-être social.*
($ over 4 years, 2003-2007, no financial award to WDF)

Principal applicant: Bismar, T
Co-applicants: Foulkes, WD; Rubin, M.A
Prostate Cancer Research Foundation of Canada (PCRFC): *Defining aggressive phenotype of prostate cancer using a multiplex of 12 gene model*
($ over 2 years, 2005-2007)

Principal applicant: Narod, S
Co-applicants: Foulkes WD
CBCRI(Canada): *Risk factor analysis of hereditary breast and ovarian cancer*
($ over 5 years, 2004-2009)

CLINICAL RESEARCH FELLOWS

Pierre Chappuis MD (1998-2001)
Research: Cancer Genetics: in particular, treatment and outcome in hereditary breast cancer
Current position: Head, Hereditary cancer clinics, Divisions of Oncology and Medicine, University Hospital of Geneva, Switzerland.

Zhi Qi Yuan MD (1998-2000)
Research: Genetics of Colorectal Cancer
Current position: Instructor, Albert Einstein College of Medicine, Bronx, New York.

David Farber MD (2001-2002)
Research: Genetics of Colorectal Cancer
Current position: Staff Gastroenterologist, Cité de la Santé, Laval, Québec

John Goffin MD (2001-2002)
Research : Survival following breast cancer in *BRCA1/2* mutation carriers
Current position: Instructor, Tufts University Medical Center, Boston, MA

Rami Younan MD (2003)
Research: Genomic deletions in *MLH1* and MSH2
Current position: Staff surgeon, Université de Montréal

Polymnia Galiatsatos (2005)
Research: Genetics of Colorectal Cancer
Current Position: Staff gastroenterologist, SMBD-Jewish General Hospital

STUDENTS

Sophie Sun, MSc. Title: *CDKN2A/p16 and familial cancer*. FCAR scolar, 1995-1996.
Current position: Oncology Fellow, University of British Columbia.

Lucie Dupuis, MSc. Title: The incidence of cancer in the first degree relatives of women diagnosed with endometrial cancer before age 55. Genetic counselling Master's project (Brandeis University, MA, USA, 1998. *NB* Ms. Dupuis obtained permission to work with me while at Brandeis).
Current position: Genetic Counsellor, Hospital for Sick Children, Toronto, Ontario.

Isabelle Thiffault, MSc student, 2002-2004:Towards a molecular understanding of proteus syndrome.
Current Position: PhD student, Université de Montréal.

Susan McVety, MSc student, 2003- 2005: Characterisation of cDNA deletions in *MLH1* and *MSH2*.
Current Position: Laboratory Technician.

Ioli Makriyianni, MSc student, 2003-2005: Mitochondrial and somatic mutations in hereditary breast cancer.

Tayma Khalil, MSc student 2005-: CDC4, cyclin E and hereditary breast cancer.

McGILL UNIVERSITY SUMMER STUDENTS
(2 month projects)

Tamar Flanders 1996. Project: Familial studies of colorectal and endometrial cancer*
Kevin Sanders 1996. Project: Familial risks of Thyroid Cancer and Breast/Thyroid cancer*
Nathalie Ng Cheong 1997. Project: *PTEN* mutations in familial cancer*
Marie-Noelle Hébert-Blouin 1998. Project: *GSTT1* and risk of head and neck cancer*
Nicola Matthews 1998. Project: Lobular breast cancer and familial cancer risk*
Karen Buzaglo 2000. Project: Familial factors in fallopian tube cancer*
Maral Ouzounian 2000. Project: Germ-line mutations in hereditary breast cancer
Annick Wong 2002. Project: Claudins and cancer*

*work published as a result of their project

McGILL UNIVERSITY INDEPENDENT STUDIES STUDENTS
(3—4 credits)

Kiersten Henderson 1999 Project: Association studies in thyroid cancer*
Ayesha Islam 1999 Project: BRCA1/2 mutations in pancreas cancer among French-Canadians
Elsa Lanke 1999 Project: Thyroid cancer/Gastric Cancer genetics*
Vanessa Rossigny 2003 Project: CHEK2 and breast cancer in the Ashkenazim
David Novak 2005 Project**:** CHEK2 and breast cancer in French Canadians

*work published as a result of their project

COMPLETED POST DOCTORAL FELLOWSHIPS

Ala-Eddin Moustafa PhD (1999-2002)
Research: Genetic factors in squamous cell carcinoma of the head and neck
Current position: Assistant Professor, Department of Oncology, McGill University

Long Qi Chen MD PhD (2004-2005)
Research: SNP Discovery in CHEK2
Current position: Professor of Cardiothoracic Surgery, Szechuan Province, China.

MEMBERSHIPS

1984	General Medical Council: registration number 2921080
1987	Royal College of Physicians (UK)
1996	Collège des Médecins du Quebec, licence number 96-449
2000	Association of Medical Geneticists of Québec (by examination)

PROFESSIONAL SOCIETIES
British Medical Association
British Society of Human Genetics
American Society of Human Genetics

McGILL UNIVERSITY DEPARTMENTAL COMMITTEES

2001-	Member, Curriculum Committee, Department of Human Genetics
2001-	Member, Fellowship Committee, Department of Human Genetics
2001-	Member, Standing Committee, Department of Human Genetics
2001-	Member, Management Committee, Department of Oncology

Ph.D. DEFENCE /M.Sc. REFEREE

PhD, McGill Dept. Biology
Ronald Lafreniere, June 17, 1997.

MSc, McGill Dept. Epidemiology and Statistics
Hela Makni, April 2000

MSc, McGill Dept. Biology
Sahar Sibani, January 2001

MSc, McGill Dept Epidemiology and Statistics
Nooshin Ahmadi Pour, January 2003

PhD, University of Toronto Faculty of Medicine
Alexander Liede, February 2003

PhD, McGill Dept. Experimental Medicine
Kevin Little, November 2004

MSc, University of Toronto, Faculty of Medicine
Sean Cleary, December 2004

INTERNATIONAL CONFERENCE ORGANISER

First International Symposium on Hereditary Breast and Ovarian Cancer, Montreal Oct 19-21, 2005. (www.odon.ca/brca/). Co-sponsored by the Program in Cancer Genetics and the Hereditary Breast and Ovarian Cancer Foundation (www.hboc.ca). Role: Scientific Director of Conference.

INTERNATIONAL COMMITTEES etc

Cancer Genetics Abstract Referee, ASHG meeting, San Francisco, CA, 1999.
Co-Chair, Breast Cancer Genetics Session, ASHG, Denver, CO, 1998.
Member, Steering Committee, International Prostate Cancer Genetics Collaborative Group (representing Eastern Canada) 1997-
Writing committee, Cancer Genetics Certification Examination, Institute for Clinical Evaluation, American Board of Internal Medicine, Philadelphia, PA 1999-2000
Scientific Organising Committee, UICC International Conference on Familial Cancer, Oklahoma City, OK, June 4-6, 2003.

NATIONAL and INTERNATIONAL PEER-REVIEW GRANT COMMITTEE etc

National Cancer Institute of Cancer, Epidemiology panel, 1997-2000
Canadian Breast Cancer Research Initiative, IDEA grant panel, 2002-2003

Canadian Institute for Health Research, Genetics Panel, 2003-
ad hoc external reviewer of grants for MRC (Canada) (6), Alberta Heritage Fund for Medical Research (1), Cancer Research Campaign (UK) (5) Research Grants Council of Hong Kong (3), Yorkshire Cancer Research (1).
Tenure review, Independent Investigator, National Human Genome Research Institute, January 2001.
Promotion review (to Assistant Professor) Memorial Sloan-Kettering Cancer Center, June 2001.
Tenure review (to Associate Professor), University of Vermont, September 2002
Tenure review (to Full Professor) Memorial Sloan-Kettering Cancer Center, January 2003
Tenure review (to Full Professor) Sloan Kettering Institute and Memorial Sloan-Kettering Cancer Center, January 2003
Promotion review (to Clinical Assistant Professor), Ohio State University, July 2003
Promotion review (to Reader), University of London, May 2004
Promotion review (to Clinical Assistant Professor), Ohio State University, August 2004
Promotion review (to Clinical Assistant Professor), Ohio State University, August 2004
Promotion review (to Clinical Associate Professor), Ohio State University, April 2005
Promotion review (to Professor), University of London, April 2005

PROVINCIAL EXPERT COMMITTEE

Member, Advisory Board, Conseil d'Évaluation des technologies de la santé du Québec, 1999-

NIH CANCER WORKSHOP

Invited attendee, NCI/NIDCFR/NIDCD Head and Neck Cancer Workshop, Bethesda, Maryland, February 21-23, 1999

VISITING LECTURESHIP

Samuel Riven Lectureship, Vanderbilt University, Tennessee, USA, September 1-3, 1999.

TEACHING

a) NATIONAL

Workshop on the Genetics of Cancer, Royal College of Physicians of Canada, Montreal, September 23, 1999.

b) McGILL UNIVERSITY

1) Environmental Carcinogenesis (516-614B MSc program) 1996-1999, 2003, 2005 (One two-hour session)

2) Unit 8 small group teaching in medical genetics (medical students) 1997-

(One 2 hour lecture and 4 small group sessions, 3 hours each)

3) Genetics course (biology BSc students) 1998-1999
(Six one hour lectures and one 2 hour pre-exam session)

4) Unit 1 teaching (medical students) 2001-
(one two hour seminar)

5) Special Topics in Epidemiology and Biostatistics: Introduction to genetic epidemiology and statistical methods for human genetics (513-670A, Department of Epidemiology and Biostatistics) (2001-2, one 1 hour seminar)

6) ICM whole class oncology teaching: Three lectures on the prevention of Colorectal cancer (2002-2004)

7) Experimental and Clinical Oncology #5160635D: Cancer Genetics-1.5 hour seminar (2002-)

8) Inherited Cancer Syndromes, 521-690B, Department of Human Genetics: Four 2 hour lectures (2003-)

c) HOSPITAL

1) Genetics in Oncology Lecture (Residents) 1998-1999
(1.5 hour teaching session residents, SMBD-Jewish General Hospital)
2) Hereditary Breast Cancer (Surgical Residents) November 2005
(1 hour teaching session surgical residents, RVH)
3) Hereditary Breast Cancer (Surgical Residents) October 2006
(1 hour teaching session surgical residents, RVH)

HOSPITAL COMMITTEE

Montreal General Hospital Research Ethics Committee member, 1998-2004

PUBLICATIONS (* denotes WF corresponding author if more than one author)

a) Peer Reviewed Articles

1. Levi S, Beardshall K, Swift I, Foulkes WD, Playford R, Ghosh P and Calam, J: Antral Helicobacter pylori, hypergastrinaemia, and duodenal ulcers: effect of eradicating the organism. *Br Med J*, 299: 1504-5, 1989.
2. Campbell IG, Jones T, Foulkes WD, and Trowsdale J: Folate Binding Protein is a marker for ovarian cancer. *Cancer Res*, 51: 5529-5538, 1991.

3. Campbell IG, Freemont PS, Foulkes WD, and Trowsdale J: An ovarian tumour marker with homology to vaccinia virus contains an IgV-like region and multiple transmembrane domains. *Cancer Res*, 52: 5416-5420, 1992.

4. Foulkes WD, Campbell IG, Stamp GWH and Trowsdale J: Loss of heterozygosity and amplification of chromosome 11 in human ovarian cancer. *Br J Cancer*, 67: 268-273, 1993.

5. Foulkes WD, Ragoussis J, Stamp GWH, Allan GJ and Trowsdale J: Frequent loss of heterozygosity on chromosome 6 in human ovarian carcinoma. *Br J Cancer*, 67: 551-559, 1993.

6. Foulkes WD, Black DM, Stamp GWH, Solomon E and Trowsdale J: Very frequent loss of heterozygosity on chromosome 17 in ovarian carcinoma. *Int J Cancer*, 54: 220-225, 1993.

7. Naylor MS, Stamp GWH, Foulkes WD, Eccles DM and Balkwill FR: Tumor Necrosis Factor and its receptors in human ovarian cancer-potential role in disease progression. *J Clin Invest*, 91: 2194-2206, 1993.

8. Allan GJ, Cottrell S, Trowsdale J and Foulkes WD: Loss of heterozygosity on chromosome 5 in sporadic ovarian carcinoma is a late event and is not associated with mutations in APC at 5q21-22. *Human Mutation*, 3: 283-291, 1994.

9. Foulkes WD, Englefield P and Campbell IG: Mutation analysis of RASK and the 'FLR exon' of NF1 in sporadic ovarian carcinoma. *Eur J Cancer*, 30A: 528-530, 1994.

10. Campbell IG, Nicolai HM, Foulkes WD, Stamp GWH, Senger G, Allan GJ, Boyer CM, Jones K, Bast RC Jr, Solomon E, Trowsdale J and Black DM: A novel gene encoding a B-Box protein within the BRCA1 region at 17q21.1. *Hum Mol Genet*, 3: 589-594, 1994.

11. Campbell IG, Foulkes WD, Senger G, Trowsdale J, Garin-Chesa P and Rettig WJ: Molecular cloning of the B-CAM cell surface glycoprotein of epithelial cancers: a novel member of the immunoglobulin super-family. *Cancer Res*, 54: 5761-5765, 1994.

12. Englefield P, Foulkes WD and Campbell IG: Loss of heterozygosity on chromosome 22q in ovarian carcinoma is distal to and is not accompanied by mutations in NF2 at 22q12. *Br J Cancer*, 70: 905-907, 1994.

13. Foulkes WD, Stamp GWH, Afzal S, Lalani N, McFarlane C, Trowsdale J and Campbell IG: MDM2 amplification is uncommon in ovarian carcinoma irrespective of TP53 status. *Br J Cancer*, 72: 883-8, 1995.

14. Foulkes WD, Brunet J-S, Kowalski LP, Narod SA and Franco EL: Family history is a risk factor for squamous carcinoma of the head and neck in Brazil: a case-control study. *Int J Cancer*, 63: 769-773, 1995.

15. Campbell, Foulkes WD, Beynon G, Davis M and Englefield P: LOH and mutation analysis of CDKN2 in primary human ovarian cancers. *Int J Cancer*, 63: 222-225, 1995.

16. Phelan CM, Lancaster JM, Tonin P, Gumbs C, Carter R, Ghadirian P, Perret C, Moslehi R, Dion F, Faucher M-C, Dole K, Karimi S, Foulkes WD, Lounis H, Warner E, Goss P,

Anderson D, Larsson C, Narod SA and Futreal PA: Mutation analysis of the BRCA2 gene in 49 site-specific breast cancer families. *Nature Genetics*, 13:121-123, 1996.

17. Afzal S, Lalani EN, Foulkes WD, Boyce B, Tickle S, Cardillo MR, Baker T, Pignatelli M and Stamp GWH: Matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 espression and synthetic matrix metalloproteinase-2 inhibitor binding in ovarian carcinomas and tumour cell lines. *Laboratory Invest*, 74: 406-421, 1996.
18. Bryan EJ, Watson RH, Davis M, Hitchcock A, Foulkes WD and Campbell IG: Localization of an ovarian cancer tumor suppressor gene to a 0.5cM region between D22S284 and CYP2D, on chromosome 22q. *Cancer Res*, 56: 719-721, 1996.
19. Davis M, Hitchcock A, Foulkes WD and Campbell IG: Refinement of two chromosome 11q regions of heterozygosity in ovarian cancer. *Cancer Res*, 56: 741-744, 1996.
20. Foulkes WD, Bolduc N, Lambert D, Ginsburg O, Yandell DW, Tonin P and Narod SA: Increased incidence of cancer in first degree relatives of women with double primary carcinomas of the breast and colon. *J Med Genet*, 33: 534-539, 1996.
21. Foulkes WD, Brunet J-S, Sieh W, Shenouda G, Black MJ and Narod SA: Familial risks of squamous cell carcinoma of the head and neck. *Br Med J*, 313: 716-721, 1996.
22. Tonin P, Weber B, Offit K, Couch F, Rebbeck TR, Neuhausen S, Godwin AK, Daly M, Wagner-Costalos J, Berman D, Grana G, Fox E, Kane MF, Kolodner RD, Krainer M, Haber DA, Struewing JP, Warner E, Rosen B, Lerman C, Peshkin B, Norton L, Serova O, Foulkes WD, Lynch HT, Lenoir GM, Narod SA and Garber JE: Frequency of recurrent BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer families. *Nature Med*, 2:1179 -1183, 1996.
23. Milner BJ, Hosking L, Sun S, Haites NE, Foulkes WD: Polymorphisms in $P21^{CIP1/WAF1}$ are not correlated with TP53 status in sporadic ovarian tumours. *Eur J Cancer*, 32A: 2360-2363, 1996.
24. Cutler C, Foulkes WD, Brunet J-S, Flanders T, Shibata H and Narod SA: Cutaneous malignant melanoma is uncommonly associated with a family history of melanoma. *Melanoma Res*, 6: 435-440, 1996.
25. Foulkes WD, Buu PN, Filiatrault D, Leclerc J-M and Narod SA: An excess of congenital abnormalities in French-Canadian children with neuroblastoma: A case series study from Montreal. *Med Pediatr Oncol*, 29: 272-79, 1997
26. Karp SE, Tonin PN, Bégin LR, Martinez JJ, Zhang JC, Pollak MN and Foulkes WD: Influence of BRCA1 mutations on nuclear grade and estrogen receptor status on breast carcinoma in Ashkenazi Jewish women. *Cancer*, 80: 435-441, 1997.
27. Foulkes WD, Wong N, Brunet J-S, Narod SA, Bégin LR, Zhang JC, Martinez JJ, Tonin PN, Karp SE, Pollak MN. Germ-line BRCA1 mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer. *Clin Cancer Res*, 3: 2465-2470, 1997
28. Sun S, Pollock P, Liu L, Karimi S, Jothy S, Milner BJ, Renwick A, Lassam NJ, Hayward NK, Hogg D, Narod SA and Foulkes WD: CDKN2A mutation in a non-

FAMMM kindred with cancers at multiple sites results in a functionally abnormal protein. *Int J Cancer*, 73: 531-536, 1997.

29. Bignell GR, Canzian F, Shayeghi M, Stark M, Shugart YY, Biggs P, Mangion J, Hamoudi R, Rosenblatt J, Buu P, Sun S, Stoffer SS, Goldgar DE, Romeo G, Houlston RS, Narod SA, Stratton MR and Foulkes WD: A familial non-toxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial non-medullary thyroid cancer. *Am J Hum Genet*, 61: 1123-1130, 1997.
30. Eeles RA, Simard J, Teare D, Edwards S, Durocher F, Badzioch M, Hamoudi R, Gill S, Biggs P, Dearnaley D, Arden-Jones A, Dowe A, Shearer R, Ford D, Amos C, The CRC/BPG Familial Prostate Cancer Study Collaborators, Ghadirian P, Aprikian A, Norman R, McLellan D, Labrie F, Narod SA, Easton D and Foulkes WD: Linkage analysis of chromosome 1q markers in 136 prostate cancer families. *Am J Hum Genet*, 62: 653-658, 1998.
31. Brunet J-S, Ghadirian P, Rebbeck TR, Lerman CE, Garber JE, Tonin PN, Abrahamson J, Foulkes WD, Daly M, Wagner-Costalas J, Godwin A, Olopade F, Moslehi R, Liede A, Futreal PA, Weber B, Lenoir GM, Lynch HT and Narod SA: The effect of smoking on breast incidence in BRCA1 and BRCA2 carriers. *J Natl Canc Inst*, 90: 761-766, 1998.
32. Pollock PM, Spurr N, Bishop DT, Newton-Bishop J, Gruis N, Goldstein AM, Tucker MA, Foulkes WD, Barnhill R, Haber D, Fountain J and Hayward NK: Haplotype analysis of 2 recurrent CDKN2A mutations in 10 melanoma families from three continents-evidence for common founders. *Hum Mutation*, 11: 424-431, 1998.
33. Godard B, Foulkes WD, Provencher D, Brunet J-S, Tonin PN, Mes-Masson, A-M, Narod SA and Ghadirian P: Risk factors for familial and sporadic ovarian cancer among French-Canadians: a case-control study. *Am J Obs Gyne*, 179: 403-410, 1998.
34. Kerr B, Foulkes WD, Cade D, Hadfield L, Hopwood P, Serruya C, Hoare F, Narod SA and Evans DG: False family history of breast cancer in the family cancer clinic. *Eur J Surg Oncol*, 24: 275-279, 1998.
35. Tonin PN, Mes-Masson A-M, Futreal PA, Morgan K, Mahon M, Foulkes WD, Cole DEC, Provencher D, Ghadirian P and Narod SA: Founder BRCA1 and BRCA2 mutations in French Canadian breast and ovarian cancer families. *Am J Hum Genet*, 63: 1341-1351, 1998.
36. Pal T, Flanders T, Lehman M, McMillan A, Brunet J-S, Narod SA and Foulkes, WD: Genetic implications of double primary cancers of the colorectum and endometrium. *J Med Genet*, 35: 978-984, 1998.
37. de Andrade M, Amos, CI and Foulkes WD: Segregation analysis of squamous cell carcinoma of the head and neck: evidence for a major gene determining risk. *Ann Hum Genet*, 62: 505-510, 1998.
38. Wang Z-J, Churchman M, Campbell IG, Xu W-H, Yan Z-Y, McCluggage WG, Foulkes WD and Tomlinson IPM: Allele loss and mutation screen at the Peutz-Jeghers (LKB1) locus (19p13.3) in sporadic ovarian tumours. *Br J Cancer*, 80: 70-72, 1999.

39. Pereira P, Stanton V, Jothy S, Tomlinson IPM, Foulkes WD and Rozen R: Loss of heterozygosity of methylenetetrahydrofolate reductase in colon carcinomas. *Oncology Reports*, 6: 597-599, 1999.

40. Warner E, Foulkes WD, Goodwin P, Meschino W, Blondal J, Patterson C, Ozcelik H, Goss P, Allingham-Hawkins D, Hamel N, Di Prospero L, Contiga V, Serruya C, Klein M, Moslehi R, Honeyford J, Liede A, Glendon G, Brunet J-S and Narod S: Prevalence and penetrance of BRCA1 and BRCA2 mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst*, 91: 1241-1247, 1999.

41. Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. *J. Natl Cancer Instit*, 91: 1310-1316, 1999 (WDF was one of the many who contributed data to this publication).

42. Yuan ZQ, Bégin LR, Wong N, Brunet J-S, Trifiro M, Gordon PH, Pinsky L and Foulkes WD: The effect of the I1307K APC polymorphism on the clinicopathological features and natural history of breast cancer. *Br J Cancer*, 81: 850-854, 1999.

43. Jernström H, Lerman C, Ghadirian P, Lynch H, Weber B, Garber J, Daly M, Olopade O, Foulkes WD, Warner E, Brunet J-S and Narod SA. Pregnancy increases the risk of early breast cancer in BRCA1 and BRCA2 carriers. *Lancet*, 354:1846-1850, 1999.

44. Hamel N, Black MJ, Ghadirian P and Foulkes WD: No association between p53 codon 72 polymorphism and risk of squamous cell carcinoma of the head and neck. *Br J Cancer*, 82: 757-759, 2000.

45. Xu JF and International Consortium for Prostate Cancer Genetics (ICPCG). Combined Analysis of Hereditary Prostate Cancer Linkage to 1q24-25: Results from 772 Hereditary Prostate Cancer Families from the International Consortium for Prostate Cancer Genetics. *Am J Hum Genet*, 66: 945-957, 2000 (WDF is a member of the ICPCG writing committee for this paper).

46. Foulkes WD, Chappuis PO, Wong N, Brunet J-S, Vesprini D, Rozen F, Yuan ZQ, Pollak MN, Kuperstein G, Narod SA and Bégin LR. Primary node negative breast cancer in BRCA1 mutation carriers has a poor outcome. *Ann Oncol*, 11: 307-313, 2000.

47. Rahman N, Arbour L, Houlston R, Bonaïti-Pellié C, Abidi F, Tranchemontagne J, Ford D, Narod SA, Pritchard-Jones K, Foulkes WD, Schwartz C and Stratton MR. Penetrance of mutations in the familial Wilms tumor gene, FWT1. *J Natl Cancer Inst*, 92: 650-652, 2000.

48. Liu G, Ghadirian P, Vesprini, D, Hamel N, Paradis A-J, Lal G, Gallinger S, Narod SA and Foulkes WD. Polymorphisms in GSTM1, GSTT1 and CYP1A1 and risk of pancreatic cancer. *Br J Cancer*, 82: 1646-9, 2000.

49. Kuperstein G, Foulkes WD, Ghadirian P, Hakimi J and Narod SA. A rapid fluorescent multiplexed-PCR analysis (FMPA) for founder mutations in the BRCA1 and BRCA2 genes. *Clin Genet*, 57: 213-220, 2000.

50. Rapley E, Barfoot R, Bonaiti-Pellie C, Chompret A, Foulkes WD, Perusinghe N, Reeve A, Royer-Pokora B, Schumacher V, Shelling A, Skeen J, de Tourreil S, Weirich A, Pritchard-Jones K, Stratton MR, Rahman N. Evidence for susceptibility genes to

familial Wilms tumour in addition to WT1, FWT1and FWT2. *Br J Cancer*, 83: 177-83, 2000.

51. Yuan ZQ, Chong GL, Thompson-May S, Trifiro M, Khandjian EW, Rousseau F, Yandell D, McNamara E, Gordon PH and Foulkes WD. Analysis of the hMLH1 and hMSH2 genes in three Quebec families with Hereditary Non-Polyposis Colorectal Cancer. *Ann Roy Coll Phys Surg Canada*, 33: 287-291, 2000.
52. Metcalfe K, Liede A, Hoodfar E, Scott A, Foulkes WD and Narod SA: An evaluation of needs among female BRCA1 and BRCA2 mutation carriers undergoing genetic counselling. *J Med Genet*, 37: 866-874, 2000.
53. Chappuis PO, Kapusta L, Bégin LR, Wong N, Brunet J-S, Narod SA, Slingerland J and Foulkes WD: Germline BRCA1/2 mutations and $p27^{Kip1}$ protein levels independently predict outcome after breast cancer. *J Clin Oncol*, 18: 4045-4052, 2000.
54. Thompson D, Easton D and the Breast Cancer Linkage Consortium. Variations in Cancer Risks by mutation position in BRCA2 mutation carriers. *Am J Hum Genet*, 68: 410-9, 2001. (WDF was one of the many who contributed data to this publication).
55. Tonin PN, Perret C, Lambert J, Paradis A-J, Kantemiroff T, Benoit M-H, Martin B, Foulkes WD, Ghadirian P. Founder BRCA1 and BRCA2 mutations in early-onset French Canadian breast cancer cases unselected for family history. *Int. J Cancer*, 95: 189-193, 2001.
56. Manning AP, Abelovich D, Ghadirian P, Lambert JA, Frappier D, Provencher D, Robidoux A, Peretz T, Narod SA, Mes-Masson A-M, Foulkes WD, Wang T, Morgan K, TM Fujiwara, Tonin PN. Haplotype analysis of BRCA2 8765delAG mutation carriers in French Canadian and Yemenite Jewish Hereditary Breast Cancer Families. *Human Heredity*, 52: 116-120, 2001.
57. Pal T, Hamel N, Vesprini D, Sanders K, Mitchell M, Quercia N, Ng Cheong N, Murray A, Foulkes WD and Narod SA. Double primary cancers of the breast and thyroid in women: molecular analysis and genetic implications. *Familial Cancer*, 1: 17-24, 2001.
58. Satagopan JM, Offit K, Foulkes WD, Robson ME, Wacholder S, Eng CM, Karp SE, Begg CB. The lifetime risk of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiology Biomarkers and Prevention*, 10: 467-73, 2001.
59. Greenblatt MS, Chappuis PO, Bond JP, Hamel N and Foulkes WD. TP53 mutations in BRCA1/2-related breast cancer: distinctive spectrum and structural distribution. *Cancer Research*, 61: 4092-97, 2001.
60. Runnebaum IB, Wang-Gohrke S, Vesprini D, Kreienberg R, Lynch H, Moslehi R, Ghadirian P, Weber B, Godwin AK, Risch H, Garber J, Lerman C, Olapade OI, Foulkes WD, Karlan B, Warner E, Rosen B, Rebbeck T, Tonin P, Dubé M-P, Kieback DG, Narod SA. Progesterone receptor variant increases ovarian cancer risk in BRCA1 and BRCA2 mutation carriers who were never exposed to oral contraceptives. *Pharmacogenetics*, 11: 1-4, 2001.
61. Chappuis PO, Hamel N, Paradis A-J, Deschênes J, Robidoux A, Potvin C, Cantin J, Tonin PN, Ghadirian P, Foulkes WD. Prevalence of founder BRCA1 and BRCA2

mutations in unselected French Canadian women with breast cancer. *Clin Genet*, 59: 418-423, 2001.

62. Bevan S, Pal T, Greenberg CR, Green H, Wixey J, Bignell G, Narod SA, Foulkes WD, Stratton MR and Houlston RS. A comprehensive analysis of MNG1, TCO1, fPTC, PTEN, RET, TSHR and TRKA in Familial Non-Medullary Thyroid Cancer: Confirmation of linkage to TCO1. *J Clin Endocrinol Metab*, 86: 3701-4, 2001.
63. Julian-Reynier C, Bouchard L, Evans DGR, Eisinger F, Foulkes WD, Kerr B, Blanquaert, Moatti J-P and Sobol H. Women's attitudes towards preventive strategies for Hereditary Breast/Ovarian cancer risk differ from one country to another: differences between Manchester (UK), Marseilles (F) and Montreal (Ca). *Cancer*, 92: 959-68, 2001.
64. Elhaji YA, Gottleib B, Lumbroso R, Beitel LK, Foulkes WD, Pinsky L and Trifiro M. The Polymorphic CAG Repeat of the Androgen Receptor Gene: A Potential Role in Breast Cancer in Women over 40. *Breast Cancer Research and Treatment*, 70:109-16, 2001.
65. Pal T, Vogl FD, Chappuis PO, Tsang R, Brierley J, Renard H, Sanders K, Kantemiroff T, Bagha S, Goldgar DE, Narod SA and Foulkes WD. Increased risk for non-medullary thyroid cancer (NMTC) in the first-degree relatives of prevalent cases of NMTC: a hospital-based study. *J Clin Endocrinol Metab*, 86: 5307-12, 2001
66. Jefferies S, Edwards SM, Hamoudi R, A'Hern R, Foulkes WD, Goldgar D, MPT collaborators and Eeles R. No germline mutations in CDKN2A (p16) in patients with squamous cell cancer of the head and neck and second primary tumours. *Br J Cancer*, 85: 1383-6, 2001.
67. Yuan ZQ, Gottlieb B, Beitel LK, Wong N, Gordon PH, Wang Q, Puisieux, A, Foulkes WD and Trifiro M. Polymorphisms and HNPCC: PMS2-MLH1 protein interactions diminished by 'single nucleotide polymorphisms'. *Human Mutation*, 19: 108-13, 2002.
68. Ghadirian P, Liu G, Gallinger S, Schmocker B, Paradis A-J, Lal G, Brunet J-S, Foulkes WD and Narod SA. Family history is a risk factor for pancreatic cancer. *Int J Cancer*, 97: 807-810, 2002.
69. Moustafa A-E, Alaoui-Jamali MA, Batist G, Hernadez-Perez M, Serruya C, Alpert L, Black MJ, Sladek R and Foulkes WD. Identification of genes associated with head and neck carcinogenesis by cDNA microarray comparison between matched normal and squamous cell carcinoma cells. *Oncogene*, 21: 2634-2640, 2002.
70. Hutter P, Wijnen J, Rey-Berthod C, Thiffault I, Verkuijlen P, Farber D,Hamel N, Bapat B, Thibodeau SN, Burn J, Wu J, MacNamara E, Heinimann K, Chong G and Foulkes WD. An MLH1 haplotype is over-represented on chromosomes carrying an HNPCC predisposing mutation in MLH1. *J Med Genet*, 39: 323-327, 2002.
71. Laazari K, Sutton M, Ghadirian P, Scott A, Paradis A-J, Tonin PN and Foulkes WD. Is there are correlation between the structure of hair and breast cancer or BRCA1/2 mutations? *Phys Med Biol*, 47: 1623-1632, 2002.
72. Foulkes WD, Thiffault I, Gruber SB, Horwitz M, Hamel N, Lee C, Shia J, Markowitz A, Figer A, Friedman E, Farber D, Greenwood CMT, Bonner JD, Walsh T, Marcus V,

Tomsho L, Nafa K, Gebert J, Bressac-de Paillerets B, Gregersen PK, Weitzel J, Macrae FA, Gaff CL, Gordon PH, MacNamara E, King M-C, Hampel H, de la Chapelle A, Boyd J, Offit K, Rennert G, Chong G and Ellis NA. The founder mutation MSH2*1906G>C is an important cause of Hereditary Non-Polyposis Colorectal Cancer in the Ashkenazi Jewish population. *Am J Hum Genet*, 71: 1395-1412, 2002.

73. Straume O, Chappuis PO, Salvesen HB, Halvorsen OJ, Goffin J, Bégin LR, Foulkes WD, Akslen LA. Prognostic importance of Glomeruloid Microvascular Proliferation indicates an aggressive angiogenic phenotype in human cancers. *Cancer Res*, 62: 6308-6811, 2002.

74. Narod SA, Dubé M-P, Klijn J, Lubinski J, Lynch HT, Ghadirian P, Provencher D, Heimdal K, Moller P, Isaacs C, Weber B, Friedman E, Gershoni-Baruch R, Rennert G, Pasini B, Wagner T, Daly M, Garber JE, Neuhausen S, Robson ME, Offit K, Ainsworth P, Olsson H, Evans DGR, Osborne M, Couch F, Foulkes WD, Warner E, Kim-Sing C, Olopade O, Tung N, Saal HM, Weitzel J, Merajver S, Gauthier-Villars M, Jernstrom H, Sun P, Brunet J-S. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 carriers. *J Natl Cancer Inst*, 94: 1773-1779, 2002.

75. Karakiewicz PI, Foulkes WD, Tanguay S, Elhilali MM, Aprikian AG. Familial prostate and breast cancer in men treated with prostatectomy for prostate cancer: a population based case-control study. *J Urol*, 169: 240-4, 2003.

76. Goffin JR, Chappuis PO, Bégin LR, Wong N, Brunet J-S, Hamel N, Paradis A-J, Boyd J, Foulkes WD. The impact of germ-line BRCA1 mutations and over-expression of p53 on prognosis and response to treatment following breast cancer: 10 year follow up data. *Cancer*, 97: 527-536, 2003.

77. Guillem JG, Rapaport BS, Kirchhoff T, Kolchana P, Nafa K, Glogowski E, Finch R, Huang H, Foulkes WD, Markowitz A, Ellis NA and Offit K. A636P is associated with early-onset colorectal cancer in Ashkenazi Jews. *J Am Coll Surg*, 196:222-225, 2003.

78. Goffin JR, Straume O, Chappuis PO, Brunet J-S, Bégin LR, Hamel N, Wong N, Akslen LA and Foulkes WD. Glomeruloid Microvascular Proliferation is associated with p53 overexpression, germ-line BRCA1 mutations and an adverse outcome following breast cancer. *Br J Cancer*, 89: 1031-1034, 2003.

79. Foulkes WD, Metcalfe K, Hanna W, Lynch HT, Ghadirian P, Tung N, Olopade O, Weber B, McLennan J, Olivotto IA, Sun P, Chappuis PO, Bégin LR, Brunet J-S and Narod SA. Disruption of the expected positive correlation between tumor size and nodal status in BRCA1-related breast cancer. Cancer, 98: 1569-1577, 2003.

80. Foulkes WD, Stefansson IM, Chappuis, PO Bégin LR, Goffin JR, Wong N, Trudel M and Akslen LA. Germ-line BRCA1 mutations and the basal epithelial phenotype of breast cancer. J Natl Cancer Inst, 95: 1482-1485, 2003.

81. Pollak MN, Foulkes WD. Challenges to cancer control by screening. Nat Rev Cancer, 3: 297-303, 2003.

82. Halford SE, Sawyer EJ, Lambros MB, Gorman P, Macdonald ND, Talbot IC, Foulkes WD, Gillett CE, Barnes DM, Akslen LA, Lee K, Jacobs IJ, Hanby AM, Ganesan TS,

Salvesen HB, Bodmer WF, Tomlinson IP, Roylance RR. MSI-low, a real phenomenon which varies in frequency among cancer types. J Pathol, 201: 389-394, 2003.

83. Matakidou A, Hamel N, Polpat S, Henderson K, Kantemiroff T, Harmer C, Clarke SE, Houlston RS, and Foulkes WD. Risk of non-medullary thryoid cancer influenced by polymorphic variation in the thyroglobulin gene. Carcinogenesis, 25: 369-73, 2004.
84. Edwards S, Meitz J, Eles R, Evans C, Easton D, Hopper J, Giles G, Foulkes WD, Narod S, Simard J, Badzioch M, Mahle L; International ACTANE Consortium. Results of a genome-wide linkage analysis in prostate cancer families ascertained through the ACTANE consortium. Prostate, 57: 270-9, 2003.
85. Hashibe M, Brennan P, Strange RC, Bhisey R, Cascorbi I, Lazarus P, Oude Ophuis MB, Benhamou S, Foulkes WD, Katoh T, Coutelle C, Romkes M, Gaspari L, Taioli E and Boffeta P. Meta and pooled analyses of GSTM1, GSTT1,GSTP1, and CYP1A1 genotypes and risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev, 12: 1509-17, 2003.
86. Thiffault I, Hamel N, Pal T, McVety S, Marcus VA, Farber D, Cowie S, Deschenes J, Meschino W, Odefrey F, Goldgar D, Graham T, Narod S, Watters AK, MacNamara E, Sart DD, Chong G, Foulkes WD. Germline truncating mutations in both MSH2 and BRCA2 in a single kindred. Br J Cancer, 90: 483-491, 2004.
87. Foulkes WD. BRCA1 functions as a breast stem cell regulator. J Med Genet, 41: 1-5, 2004.
88. Al Moustafa AE, Foulkes WD, Benlimame N, Wong A, Yen L, Bergeron J, Batist G, Alpert L, Alaoui-Jamali MA. E6/E7 proteins of HPV type 16 and ErbB-2 cooperate to induce neoplastic transformation of primary normal oral epithelial cells. Oncogene, 23: 350-8, 2004.
89. Bouchard L, Blancquaert I, Eisinger F, Foulkes WD, Evans G, Sobol H, Julian-Reynier C. Prevention and genetic testing for breast cancer: variations in medical decisions. Soc Sci Med, 58: 1085-96, 2004.
90. Robson ME, Chappuis PO, Satagopan J, Wong N, Boyd J, Goffin JR, Hudis C, Roberge D, Norton L, Begin LR, Offit K, Foulkes WD. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. Breast Cancer Res, 6: R8-R17, 2004.
91. Foulkes WD, Brunet JS, Stefansson IM, Straume O, Chappuis PO, Begin LR, Hamel N, Goffin JR, Wong N, Trudel M, Kapusta L, Porter P, Akslen LA. The Prognostic Implication of the Basal-Like (Cyclin high/p27low/p53+/Glomeruloid-Microvascular-Proliferation+) Phenotype of BRCA1-Related Breast Cancer *Cancer Res,* 64: 830-835, 2004.
92. Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, Tung N, Olopade OI, Weber BL, McLennan J, Olivotto IA, Begin LR, Narod SA. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. *Clin Cancer Res,* 10: 2029-34, 2004.

93. Ghadirian P, Lubinski J, Lynch H, Neuhausen SL, Weber B, Isaacs C, Baruch RG, Randall S, Ainsworth P, Freidman E, Horsman D, Tonin P, Foulkes WD, Tung N, Sun P, Narod SA. Smoking and the risk of breast cancer among carriers of BRCA mutations. *Int J Cancer,* 110: 413-6, 2004.

94. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, Olopade OI, Eisen A, Weber B, McLennan J, Sun P, Foulkes WD, Narod SA. Contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *J Clin Oncol,* 22: 2328-35, 2004.

95. Al Moustafa AE, Foulkes WD, Wong A, Jallal H, Batist G, Yu Q, Herlyn M, Sicinski P, Alaoui-Jamali MA. Cyclin D1 is essential for neoplastic transformation induced by both E6/E7 and E6/E7/ErbB-2 cooperation in normal cells. *Oncogene,* 23: 5252-6, 2004.

96. Thiffault I, Foulkes WD, Marcus VA, Farber D, Kasprzak L, MacNamara E, Wong N, Hutter P, Radice P, Bertario L, Chong G. Putative common origin of two MLH1 mutations in Italian-Quebec hereditary non-polyposis colorectal cancer families. *Clin Genet,* 66: 137-43, 2004.

97. Jernstrom H, Lubinski J, Lynch HT, Ghadirian P, Neuhausen S, Isaacs C, Weber BL, Horsman D, Rosen B, Foulkes WD, Friedman E, Gershoni-Baruch R, Ainsworth P, Daly M, Garber J, Olsson H, Sun P, Narod SA. Breast-feeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst,* 96: 1094-8, 2004.

98. Brooks-Wilson AR, Kaurah P, Suriano G, Leach S, Senz J, Grehan N, Butterfield YS, Jeyes J, Schinas J, Bacani J, Kelsey M, Ferreira P, MacGillivray B, MacLeod P, Micek M, Ford J, Foulkes WD, Australie K, Greenberg C, LaPointe M, Gilpin C, Nikkel S, Gilchrist D, Hughes R, Jackson CE, Monaghan KG, Oliveira MJ, Seruca R, Gallinger S, Caldas C, Huntsman D. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. *J Med Genet,* 41: 508-17, 2004.

99. Kotar K, Brunet JS, Moller P, Hugel L, Warner E, McLaughlin J, Wong N, Narod SA, Foulkes WD. Ratio of female to male offspring of women tested for BRCA1 and BRCA2 mutations. *J Med Genet,* 41: e103, 2004.

100. Thiffault I, Schwartz CE, Der Kaloustian V, Foulkes WD. Mutation analysis of the tumor suppressor PTEN and the glypican 3 (GPC3) gene in patients diagnosed with Proteus syndrome. *Am J Med Genet,* 1: 123-7, 2004.

101. Oros KK, Ghadirian P, Greenwood CM, Perret C, Shen Z, Paredes Y, Arcand SL, Mes-Masson AM, Narod SA, Foulkes WD, Provencher D, Tonin PN. Significant proportion of breast and/or ovarian cancer families of French Canadian descent harbor 1 of 5 BRCA1 and BRCA2 mutations. *Int J Cancer,* 112: 411-9, 2004.

102. Hope Q, Bullock S, Evans C, Meitz J, Hamel N, Edwards SM, Severi G, Dearnley D, Jhavar S, Southgate C, Falconer A, Dowe A, Muir K, Houlston RS, Engert JC, Roquis D, Sinnett D, Simard J, Heimdal K, Møller P, Maehle L, Badzioch M, The Cancer Research UK/British Association of Urological Surgeons' Section of Oncology Collaborators, Eeles RA, Easton DF, English DR, Southey M, Hopper JL, Foulkes WD, Giles GG. Macrophage Scavenger Receptor 1 (MSR1) 999C>T (R293X) mutation

and risk of prostate cancer. *Cancer Epidemiol Biomark Prevent,* 14: 397-402, 2005 (WDF is corresponding author).

103. Metcalfe KA, Lynch HT, Ghadirian P, Tung N, Olivotto IA, Foulkes WD, Warner E, Olopade O, Eisen A, Weber B, McClennan J, Sun P, Narod SA. The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers. *Obstet Gynecol Sur,* 60 (4): 235-6, 2005.

104. Metcalfe KA, Lynch HT, Ghadirian P, Tung N, Olivotto IA, Foulkes WD, Warner E, Olopade O, Eisen A, Weber B, McClennan J, Sun P, Narod SA. The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers corresponding. *Gynecol Oncol,* 96 (1): 222-6, 2005.

105. Chappuis PO, Donato E, Goffin JR, Wong N, Begin LR, Kapusta LR, Brunet JS,Porter P, Foulkes WD. Cyclin E expression in breast cancer: predicting germline BRCA1 mutations, prognosis and response to treatment. *Ann Oncol*, 16 (5): 735-742, 2005.

106. Collett K, Stefansson IM, Eide J, Braaten A, Wang H, Eide GE, Thoresen SO, Foulkes WD, Akslen LA. A Basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. *Cancer Epidemiol Biomarkers Prev,* 14 (5): 1108-12, 2005.

107. Makriyianni I, Hamel N, Ward S, Foulkes WD, Graw S. BRCA1:185delAG found in the San Luis Valley probably originated in a Jewish founder. *J Med Genet,* 42 (5): e27, 2005 (WDF is corresponding author).

108. Arnes JB, Brunet JS, Stefansson I, Begin LR, Wong N, Chappuis PO, Akslen LA, Foulkes WD. Placental cadherin and the basal epithelial phenotype of BRCA1-related breast cancer. *Clin Cancer Res,* 11(11): 4003-11, 2005.

109. Weitzel JN, Robson M, Pasini B, Manoukian S, Stoppa-Lyonnet D, Lynch HT, McLennan J, Foulkes WD, Wagner T, Tung N, Ghadirian P, Olopade O, Isaacs C, Kim-Sing C, Moller P, Neuhausen SL, Metcalfe K, Sun P, Narod SA. A comparison of bilateral breast cancers in BRCA carriers. *Cancer Epidemiol Biomarkers Prev,* 14 (6): 1534-8, 2005.

110. Zauber NP, Sabbath-Solitare M, Marotta S, Zauber AG, Foulkes WD, Chan M, Turner F, Bishop DT. Clinical and genetic findings in an Ashkenazi Jewish population with colorectal neoplasms. *Cancer,* 15: 104 (4): 719-29, 2005.

111. Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR, Meyers DA, Eeles RA, Easton DF, Foulkes WD, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Bishop T, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Hsieh CL, Halpern J, Balise RN, Oakley-Girvan I, Whittemore AS, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Thibodeau SN, McDonnell SK, Cunningham JM, Zarfas KE, Hebbring S,Schaid DJ, Friedrichsen DM, Deutsch K, Kolb S, Badzioch M, Jarvik GP, Janer M, Hood L, Ostrander EA, Stanford JL, Lange EM, Beebe-Dimmer JL, Mohai CE, Cooney KA, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela TLj, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson BA, Gronberg H, Camp NJ, Farnham J, Cannon-Albright LA, Seminara D; ACTANE Consortium. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the

international consortium for prostate cancer genetics. *Am J Hum Genet,* 77 (2): 219-29, 2005.

112. Kotsopoulos J, Lubinski J, Lynch HT, Neuhausen SL, Ghadirian P, Isaacs C, Weber B, Kim-Sing C, Foulkes WD, Gershoni-Baruch R, Ainsworth P, Friedman E, Daly M, Garber JE, Karlan B, Olopade OI, Tung N, Saal HM, Eisen A, Osborne M, Olsson H, Gilchrist D, Sun P, Narod SA. Age at menarche and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Cancer Causes Control,* 16 (6): 667-674, 2005.

113. McVety S, Younan R, Li L, Gordon PH, Wong N, Foulkes WD, Chong G. Novel genomic insertion-- deletion in MLH1: possible mechanistic role for non-homologous end-joining DNA repair. *Clin Genet,* 68 (3): 234-238, 2005.

114. Kotsopoulos J, Olopado OI, Ghadirian P, Lubinski J, Lynch HT, Isaacs C, Weber B, Kim-Sing C, Ainsworth P, Foulkes WD, Eisen A, Sun P, Narod SA. Changes in body weight and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res,* 7 (5): R833-R843, 2005.

115. Sun S, Greenwood CM, Thiffault I, Hamel N, Chong G, Foulkes WD. The HNPCC associated MSH2*1906G-->C founder mutation probably originated between 1440 CE and 1715 CE in the Ashkenazi Jewish population. *J Med Genet,* 42 (10): 766-768, 2005.

116. Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, Weber B, rebbeck T, Neuhausen SL, Ghadirian P, Foulkes WD, Gershoni-Baruch R, Friedman E, Rennert G, Wagner T, Isaacs C, Kim-Sing C, Ainsworth P, Sun P, Narod SA. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. *J Clin Oncol,* 23 (30): 7491-6, 2005.

117. Cullinane CA, Lubinski J, Neuhausen SL, Ghadirian P, Lynch HT, Isaacs C, Weber B, Moller P, Offit K, Kim-Sing C, Friedman E, Randall S, Pasini B, Ainsworth P, Gershoni-Baruch R, Foulkes WD, Klijn J, Tung N, Rennert G, Olopade O, Couch F, Wagner T, Olsson H, Sun P, Weitzel JN, Narod SA. Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. *Int J Cancer,* 117 (6): 988-91, 2005.

118. Honrado E, Osorio A, Palacios J, Milne RL, Sanchez L, Diez O, Cazorla A, Syrjakoski K, Huntsman D, Heikkila P, Lerma E, Kallioniemi A, Rivas C, Foulkes WD, Nevanlinna H, Benitez J. Immunohistochemical expression of DNA repair proteins in familial breast cancer differentiate BRCA2-associated tumors. *J Clin Oncol,* 23 (30): 7503-11, 2005.

119. van der Klift H, Wijnen J, Wagner A, Verkuilen P, Tops C, Otway R, Kohonen-Corish M, Vasen H, Oliani C, Barana D, Moller P, Delozier-Blanchet C, Hutter P, Foulkes WD, Lynch H, Burn J, Moslein G, Fodde R. Molecular characterization of the spectrum of genomic deletions in the mismatch repair genes MSH2, MLH1, MSH6, and PMS2 responsible for hereditary nonpolyposis colorectal cancer (HNPCC). *Genes Chromosomes Cancer,* 44 (2): 123-38, 2005.

120. Soravia C, Delozier CD, Dobbie Z, Berthod CR, Arrigoni E, Brundler MA, Blouin JL, Foulkes WD, Hutter P. Double frameshift mutations in APC and MSH2 in the same individual. *Int J Colorectal Dis,* 21 (1): 79-83, 2006.

121. Barker KT, Foulkes WD, Schwartz CE, Labadie C, Monsell F, Houlston RS, Harper J. Is the E133K allele of VG5Q associated with Klippel-Trenaunay and other overgrowth syndromes? *J Med Genet,* 2006 Jan 27; [Epub ahead of print]

122. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. *Am J Gastroenterol*, 101 (2): 385-98, 2006.

123. Nkondjock A, Ghadirian P, Kotsopoulos J, Lubinski J, Lynch H, Kim-Sing C, Horsman D, Rosen B, Isaacs C, Weber B, Foulkes WD, Ainsworth P, Tung N, Eisen A, Friedman E, Eng C, Sun P, Narod SA. Coffee consumption and breast cancer risk among BRCA1 and BRCA2 mutation carriers*. Int J Cancer,* 118 (1): 103-7, 2006.

124. McVety S, Li L, Gordon PH, Chong G, Foulkes WD. Disruption of an exon splicing enhancer in exon 3 of MLH1 is the cause of HNPCC in a Quebec family. *J Med Genet,* 43 (2): 153-6, 2006.

125. Minoo P, Baker K, Goswami R, Chong G, Foulkes WD, Ruszkiewicz A, Barker M, Buchanan D, Young J, Jass JR. Extensive DNA methylation in normal colorectal mucosa in hyperplastic polyposis. *Gut*. 2006 Feb 9; [Epub ahead of print]

126. Rudkin TM, Hamel N, Galvez M, Hogervorst F, Gille JJ, Moller P, Apold J, Foulkes WD. The frequent BRCA1 mutation 1135insA has multiple origins: a haplotype study in different populations. *BMC Med Genet*. 2006 Mar 1; 7 (1): 15 [Epub ahead of print]

127. McVety S, Li L, Thiffault I, Gordon P.H, MacNamara E, Wong N, Australie K, Kasprzak L, Chong G, Foulkes WD. The value of multi-modal gene screening in HNPCC in Quebec: three mutations in mismatch repair genes that would have not been correctly identified by genomic DNA sequencing alone. *Familial Cancer,* 5: 21-8, 2006.

128. Oros KK, Leblanc G, Arcand SL, Shen Z, Perret C, Mes-Masson A-M, Foulkes WD, Ghadiran P, Provencher D, Tonin PN. Haplotype analysis suggest common founders in carriers of the recurrent BRCA2 mutation, 3398delAAAAG, in French Canadian hereditary breast and/ovarian cancer families. *BMC Medical Genetics,* 7: 23, 2006

129. Li L, McVety S, Younan R, Du Sart D, Gordon PH, Hutter P, Hogervost FBL, Liang P, Chong G, Foulkes WD. Distinct patterns of Germ-Line Deletions in *MLH1* and *MLH2* : the Implication of Alu Repetitive Element in the genetic etiology of Lynch Syndrome (HNPCC). *Hum Mutations,* 27 (4): 388, 2006.

130. Friedman E, Kotsopoulos J, Lubinski J, Lynch HT, Ghadirian P, Neuhausen SL, Isaacs C, Weber B, Foulkes WD, Moller P, Rosen B, Kim-Sing C, Gershoni-Baruch R, Ainsworth P, Daly M, Tung N, Eisen A, Olopade OI, Karlan B, Saal HM, Garber JE, Rennert G, Gilchrist D, Eng C, Offit K, Osborne M, Sun P, Narod SA; the Hereditary Breast Cancer Clinical Study Group. Spontaneous and therapeutic abortions and the risk of breast cancer among BRCA mutation carriers. *Breast Cancer Res,* 2006 Mar 21;8(2):R15 [Epub ahead of print]

131. Morel CF, Thomas MA, Cao H, O'Neil CH, Pickering JG, Foulkes WD, Hegele RA. A *LMNA* splicing mutation in two sisters with severe Dunnigan-type familial partial lipodystrophy (FPLD2). *J.Clin.Endocrinol.Metab.* 2006 April 24 [Epub ahead of print]

132. Gronwald J, Tung N, Foulkes WD, Offit K, Gershoni R, Daly M, Kim-Sing C, Olsson H, Ainsworth P, Eisen A, Saal H, Friedman E, Olopade O, Osborne M, Weitzel J, Lynch H, Ghadirian P, Lubinski J, Sun P, Narod SA. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: An update. *Int J Cancer,* 118 (9); 2281-4, 2006.

133. Narod SA, Lubinski J, Ghadirian P, Lynch HT, Moller P, Foulkes WD, Rosen B, Kim-Sing C, Isaacs C, Domcheck S, Sun P; for the Hereditary Breast Cancer Clinical Study Group. Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case control study. *Lancet Oncol,* 7(5): 402-406, 2006.

134. Tischkowitz MD, Foulkes WD. The basal phenotype of BRCA1-Related Breast Cancer: Past, Present and Future. *Cell Cycle*, 5 (9): 963-7, 2006.

135. Goswami RS, Minoo P, Baker K, Chong G, Foulkes WD, Jass JR. Hyperplastic polyposis and cancer of the colon with gastrinoma of the duodenum. *Nat Clin Pract Oncol*, 3 (5): 281-4, 2006.

136. Galiatsatos P, Kasprzak L, Chong G, Jass JR, Foulkes WD. Multiple primary malignancies in a patient with situs ambiguous. *Clin Genet,* 69 (6): 528-531, 2006.

137. Foulkes WD. BRCA1 and BRCA2: Chemosensitivity, Treatment Outcomes and Prognosis. *Fam Cancer*, 5 (2): 135-142, 2006.

138. Shinto E, Baker K, Tsuda H, Mochizuki H, Ueno H, Matsubara O, Foulkes WD, Jass JR. Tumor Buds Show Reduced Expression of Laminin-5 gamma 2 Chain in DNA Mismatch Repair Deficient Colorectal Cancer. *Dis. Colon and Rectum*. 2006 June 15 [Epub ahead of print]

139. Tischkowitz M, Gologan A, Srolovitz H, Khanna M, Foulkes WD. Muir Torre syndrome and MSH2 mutations: the importance of dermatological awareness. *Br J Cancer*. 2006 Jun 20 [Epub ahead of print]

140. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, Murphy J, Ghadirian P, Friedman E, Foulkes WD, Kim-Sing C, Wagner T, Tung N, Couch F, Stoppa-Lyonnet D, Ainsworth P, Daly M, Pasini B, Gershoni-Baruch R, Eng C, Olopade OI, McLennan J, Karlan B, Weitzel J, Sun P, Narod SA, Hereditary Ovarian Cancer Clinical Study Group. Salpingo-oophorectomy and the risk of ovarian, fallopian tube and peritoneal cancers in women with BRCA1 or BRCA2 mutation. *JAMA*, 296 (2): 185-192, 2006.

141. Baker K, Chong G, Foulkes WD, Jass JR. Transforming growth factor-pathway disruption and infiltration of colorectal cancers by intraepithelial lymphocytes. *Histopathology*, 49(4): 371-380, 2006.

142. Oros, KK, Ghadirian P, Maugard CM, Perret C, Paredes Y, Mes-Masson AM, Foulkes WD, Provencher D, Tonin P. Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent. *Clin Genet*, 70(4):320-329, 2006.

143. Schaid DJ, McDonnell SK, Zarfas KE, Cunningham JM, Hebbring S, Thibodeau SN, Eeles RA, Easton DF, Foulkes WD, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Badzioch M, Bishop DT, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Guy M, Hsieh C-L, Halpern J, Balise RR, Oakley-Girvan I, Whittemore AS, Xu J, Dimitrov L,

Chang B-L, Adams TS, Turner AR, Meyers DA, Friedrichsen DM, Deutsch K, Kolb S, Janer M, Hood L, Ostrander EA, Stanford JL, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Lange EM, Ho LA, Beebe-Dimmer JL, Wood DP, Cooney KA, Seminara D, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela T LJ, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson B-A, Grönberg H, Camp NJ, Farnham J, Cannon-Albright LA, Catalona WJ, Suarez BK, Roehl KA. Pooled genome linkage scan of aggressive prostate cancer: results from the International Consortium for Prostate Cancer Genetics. *Human Genetics.* Aug 25 2006 [Epub ahead of print].

144. Kotsopoulos J, Lubinski J, Lynch H.T, Klijn J, Ghadirian P, Neuhausen SL, Kim-Sing C, Foulkes WD, Moller P, Isaacs C, Domchek S, Randall S, Offit K, Tung N, Ainsworth P, Gershoni-Baruch R, Eisen A, Daly M, Karlan B, Saal HM, Couch F, Pasini B, Wagner T, Friedman E, Rennert G, Eng C, Weitzel J, Sun P, Narod SA, Hereditary Breast Cancer Clinical Study Group. Age at first birth and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. *Breast Cancer Res.* Submitted, 2006

b) Peer-reviewed brief communications/correspondence (* corresponding author)

1. Hosking L, Trowsdale J, Nicolai H, Solomon E, Foulkes W, Stamp, G, Signer, E and Jeffreys A: A somatic *BRCA1* mutation in an ovarian tumour. *Nature Genetics* **9**:343-344, 1995.

2*. Redston M, Nathanson KC, Yuan ZQ, Neuhausen SL, Satagopan J,Wong N, Abrahamson J, Yang D, Nafa D, Antin-Ozerkis D,Ozcelik H, Andrulis I, Daly M, Pinsky L, Schrag D, Gallinger S, Kaback M, King M-C, Woodage T, Brody LC, Godwin A, Warner E, Weber B, Foulkes W and Offit K: The *APC* I1307K allele and breast cancer risk. *Nature Genetics* **20**; 13-14, 1998.

3*. Yuan ZQ, Wong N, Foulkes WD, Trifiro M, Alpert L, Manganaro F, Andreutti-Zaugg C, Iggo R, Pinsky L, Gordon P and Lasko D: A missense mutation in both *hMSH2* and *APC* in an HNPCC kindred: implications for clinical screening. *J Med Genet* **36**: 790-792, 1999.

4*. Hamel N, Manning A, Black MJ, Tonin PN and Foulkes WD: An absence of founder *BRCA2* mutations in individuals with squamous cell carcinoma of the head and neck. *Int J Cancer* (Pred. Oncol) **83**: 803-804, 1999.

5*. Foulkes WD, Brunet J-S, Warner E, Goodwin P, Meschino W, Narod SA, Goss PE and Glendon G. The importance of a family history of breast cancer in predicting the presence of a *BRCA* mutation. *Am J Hum Genet* **65**: 1776-1779, 1999.

6*. Hamel N, Karimi S, Brunet J-S, Gilfix B, Ghadirian P, Black MJ, Narod SA and Foulkes WD: Increased risk of head and neck cancer in association with *GSTT1* nullizygosity for individuals with low exposure to tobacco. *Int J Cancer* **87**: 452-454, 2000.

7. Badzioch, M, Eeles R, Leblanc G, Foulkes WD, Giles G, Edwards S, Goldgar DE, Hopper J, Bishop DT, Moller P, Heimdal K, Easton D, the CRC/BPG UK Familial

Prostate Cancer Study Group, the EU Biomed Collaborators and Simard J. Suggestive evidence for a site-specific prostate cancer gene on chromosome 1p36. *J Med Genet* **37**: 947-949, 2000.

8*. Kasprzak L, Nolet S, Gaboury L, Pavia C, Villabona C, Rivera-Fillat F, Oriola J, Foulkes WD. Familial medullary thyroid carcinoma and prominent corneal nerves associated with the germline V804M and V778I mutations on the same allele of *RET*. *J Med Genet* **38**: 784-787, 2001.

9. Foulkes WD, Brunet J-S, Wong N, Goffin J and Chappuis PO. Change in the penetrance of founder BRCA1/2 mutations? A retrospective cohort study. *J Med Genet* **39**: 407-409, 2002.

10*. Chappuis PO, Goffin J, Perret C, Wong N, Ghadirian P, Tonin PN and Foulkes WD. A significant response to neoadjuvant chemotherapy in *BRCA1/2*-related breast cancer. *J Med Genet* **39**: 608-610, 2002.

11. Maillet P, Bonnefoi H, Vaudan-Vutskits G, Pajk B, Cufer T, Foulkes WD, Chappuis PO and Sappino A-P. Constitutional Alterations of the ATM gene in early-onset sporadic breast cancer. *J Med Genet* **39**: 751-753, 2002.

12*. Kotar K, Hamel N, Thiffault I, Foulkes WD. The RNASEL 471delAAAG allele and prostate cancer in Ashkenazi Jewish men. *J Med Genet* **40**: e22, 2003.

13. Hamel N, Kotar K, Foulkes WD. Founder mutations in *BRCA1/2* are not frequent in Canadian Ashkenazi Jewish men with prostate cancer. *BMC Med Genet* **4**: 7, 2003.

14. Galiatsatos P, Kasprzak L, Chong G, Jass JR, Foulkes WD. Multiple primary malignancies in a patient with situs ambiguous. *Clin Genet,* 69 (6): 528-531, 2006.

c) Peer reviewed[#] and non-peer reviewed book chapters and reviews

1*. Foulkes W, Stamp G and Trowsdale J: *The molecular genetics of ovarian cancer*. In: Ovarian cancer 2, eds. Sharp, F., Mason, W. P. and Creasman, W.T. pp. 23-33. Chapman and Hall, London, 1992.

2. Campbell IG, Foulkes W, Jones T and Trowsdale J: *Cloning of genes encoding ovarian carcinoma-specific antigens*. In: Ovarian cancer 2, eds. Sharp, F., Mason, W.P. and Creasman, W. T. pp. 73-86. Chapman and Hall, London, 1992.

3. Naylor MS, Stamp GW, Foulkes W, Eccles D and Balkwill F: *Tumor necrosis factor: a role in ovarian cancer?* In: Tumor necrosis factor: molecular and cellular biology and clinical relevance, eds. Fiers W, Buurman WA. Pp.199-202. Karger, Basel, 1993.

4*. Foulkes WD and Trowsdale J: *Isolating tumour suppressor genes relevant to ovarian carcinoma-the role of loss of heterozygosity*. In: Ovarian Cancer 3, eds, Sharp, F., Mason WP, Berek J and Blackett AD. Pp. 23-38. Chapman and Hall, London, 1995.

5. Campbell IG, Foulkes W, Jones TA, Poels LG and Trowsdale J: *Cloning and molecular characterisation of monoclonal antibody-defined ovarian tumour antigens*. In: Ovarian Cancer 3, eds, Sharp F, Mason WP, Berek J and Blackett AD. Pp. 53-59. Chapman and Hall, London, 1995.

6*[#]. Foulkes WD and Narod SA: Hereditary breast and ovarian cancer. *Clin Invest Med* **18**:

473-484, 1995

7. Foulkes WD: A tale of four syndromes: familial adenomatous polyposis, Gardner syndrome, attenuated APC and Turcot syndrome. *Q J M* **88**: 853-863, 1995

8*. Foulkes WD and Narod SA: Screening for cancer in high risk populations. In: *Cancer screening*, ed. Miller AB, Kluwer Academic, Boston, 1996, pp165-182.

9*#. Flanders T and Foulkes WD: Pancreatic adenocarcinoma: epidemiology and genetics. *J Med Genet* **33**:889-898, 1996

10#. Foulkes WD: Inherited susceptibility to squamous cell carcinoma of the head and neck. *Ann Cancer Control Res* **7**: 492-498, 1997.

11*#. Foulkes WD, Flanders TY, Pollock PM and Hayward NK: *CDKN2A* and cancer. *Molecular Med* **3**: 4-19, 1997.

12. Foulkes WD. *BRCA1* and *BRCA2*: penetrating the clinical arena. *Lancet*, **352**: 1325-1326, 1998.

13*. Flanders TY and Foulkes WD: Cancers of the digestive system. In*: Inherited susceptibility to cancer: clinical, predictive and ethical perspectives*. Foulkes WD and SV Hodgson (eds). Cambridge University Press, 1998.

14*. Foulkes WD and Narod SA: Cancers of the breast, ovary and uterus. In*: Inherited susceptibility to cancer: clinical, predictive and ethical perspectives.* Foulkes WD and SV Hodgson (eds). Cambridge University Press, 1998.

15*. Foulkes WD and Hodgson: Late-breaking developments. In*: Inherited susceptibility to cancer: clinical, predictive and ethical perspectives*. Foulkes WD and SV Hodgson (eds). Cambridge University Press, 1998.

16*#. Kasprzak L, Foulkes WD, Shelling AN: Hereditary ovarian carcinoma. *BMJ* 318: 786-789, 1999.

17#. Jefferies S, Eeles R, Goldgar D, A'Hern R, Henk JM, Gore M, Rhys-Evans P, Archer D, Bishop K, Murkin A, Solomon E, Hodgsun S, O'Connell M, Hibbert J, Easton D and Foulkes W. The role of genetic factors in predisposition to squamous cell cancer of the head and neck. *Br J Cancer* 79: 865-7, 1999.

18*. Foulkes WD and Shelling AN: Molecular genetics of ovarian cancer: technical overview. In: *Methods in Molecular Medicine-Ovarian Cancer*. Ed Bartlett J. Humana Press, Totowa, New Jersey, pp. 273-290, 2000.

19#. Chappuis PO, Rosenblatt J and Foulkes WD: The influence of familial and hereditary factors on the prognosis of breast cancer. Ann Oncol 10: 1163-1170,1999.

20. Chappuis PO, Nethercot V and Foulkes WD: Clinico-pathological characteristics of BRCA1- and BRCA2-related breast cancer. Semin Surg Oncol 18: 287-295, 2000.

21. Chappuis PO, Ghadirian P and Foulkes WD: The role of genetic factors in the etiology of pancreatic adenocarcinoma: An update. Cancer Invest 19: 63-75, 2001.

22#. Wong N, Lasko D, Rabelo R, Pinsky L, Gordon PH and Foulkes W. Genetic counseling and interpretation of genetic tests in hereditary non-polyposis colorectal cancer syndromes Dis Colon Rectum 44: 271-9, 2001

23#. Rabelo R, Foulkes W, Gordon PH , Wong N, Yuan ZQ, Chong G, MacNamara E, Pinsky L and Lasko D. Genetic testing in high risk, hereditary colorectal cancer syndromes. Dis Colon Rectum 44: 437-46, 2001

24. Chappuis PO and Foulkes WD. Risk assessment and genetic testing. In: Ovarian Cancer, eds. Stack MS and Fishman D. (Cancer Treatment and Research series, Rosen S, series editor) Kluwer Academic, Boston. Volume 107, pages 29-59, 2002.

25. Singh R, Eeles RA, Durocher F, Simard J, Edwards S, Badzioch, Kote-Jarai Z, Teare D, Ford D, Dearnley D, Arden-Jones A, Murkin A, Dowe A, Shearer R, Kelly J, The CRC/BPG UK Familial Prostate Cancer Study Collaborators, Labrie F, Easton DF, Narod SA, Tonin PN and Foulkes WD. High risk genes predisposing to prostate cancer development: do they exist? Prostate Cancer and Prostate Diseases 3, 241-247, 2000.

26. Jefferies S and Foulkes WD. Genetic mechanisms in squamous cell carcinoma of the head and neck. Oral Oncology 37: 115-126, 2001

27. Chappuis, PO, Foulkes WD and Provencher, D. Prise en charge du syndrome du cancer du sein et de l'ovaire héréditare. Deuxième partie: Point de vue de l'oncologue et du gynécologue. Le Clinicien 16: 63-71.

28. Foulkes WD, Rosenblatt, J and Chappuis PO. The contribution of inherited factors to the clinicopathological features and behavior of breast cancer. J Mamm Biol Neoplasia 6: 453-465, 2001.

29. Shelling AN, Foulkes W. The molecular genetics of ovarian cancer. Mol Biotechnol 19: 13-28, 2001.

30*. Chappuis PO and Foulkes WD: Overview of clinical genetics of ovarian cancer. In: Familial Breast And Ovarian Cancer, eds Morrison P, Hodgson SV and Haites N. Cambridge University Press, 2002, chapter 4: pp43-72.

31*. Chappuis PO and Foulkes WD. Management of Hereditary Breast Cancer. In: Familial Breast And Ovarian Cancer, eds Morrison P, Hodgson SV and Haites N. Cambridge University Press, 2002. chapter 15: pp237-274.

32*. Chappuis PO, Stoppa-Lyonnet D, Asselin B and Foulkes WD. Natural history of hereditary breast cancer. In: Familial Breast And Ovarian Cancer, eds Morrison P, Hodgson SV and Haites N. Cambridge University Press, 2002, chapter 6: pp81-107.

33*. Foulkes WD, Lanke E, Jefferies S and Chappuis PO. Genetic susceptibility to carcinoma of the head and neck, stomach and pancreas. In: Genetic predisposition to cancer, second edition, eds. Eeles, RA, Ponder BA, Easton DF and Eng C. Chapman and Hall, 2004, chapter: pp368-391

34. Foulkes WD. BRCA1 and BRCA2: cancer treatment and outcomes. Familial Cancer, in press, 2006

d) Book co-authorship

1. A practical guide to human cancer genetics, third edition: Hodgson SV, Foulkes WD, Eng C and Maher ER. Cambridge University Press, in press.

e) Book editorship

1. Foulkes WD and SV Hodgson: Inherited susceptibility to cancer: clinical, predictive and ethical perspectives. Cambridge University Press, 1998.

f) Invited editorials and commentaries

1. Foulkes WD. *BRCA1* and *BRCA2*: penetrating the clinical arena. *Lancet*, **352**: 1325-1326, 1998.

2. Chappuis PO, Foulkes WD. Commentary on "Prevalence of *BRCA1* and *BRCA2* mutations in unselected male breast cancer patients in Canada". *Clinical Breast Cancer* **1**: 64-65, 2000.

3. Foulkes WD. Of mice and women. *Cancer Cell* 1: 11-12, 2002.

4. Foulkes WD. Polygenic or Pollyanna? *Nature Medicine*, 8: 328-330, 2002.

5. Pollak MN, Foulkes WD. Challenges to cancer control by screening. *Nat Rev Cancer*, 3: 297-303, 2003.

6. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. *Nat Rev Cancer*, 4: 665-76, 2004.

7. Rudkin TM, Foulkes WD. BRCA2: breaks, mistakes and failed separations. *Trends Mol Med*. 11(4):145-8, 2005.

g) Peer-reviewed case reports

1*. Foulkes W, Rees J and Sewry C: Influenza A and rhabdomyolsis. *J Infect* **21**: 303-304, 1990.

2*. Foulkes W, Sewry C, Calam J and Hodgson HJF: Rhabdomyolysis after intramuscular iron-dextran in malabsorption. *Ann Rheum Dis* **50**: 184-186, 1991.

3*. Druker HA, Kasprzak L, Bégin LR, Jothy S, Narod SA and Foulkes WD: A family with Graves' disease, multinodular goiter, non-medullary thyroid carcinoma and alveolar rhabdomyosarcoma. *Am J Med Genet.***72**: 30-33, 1997.

4. Liede A, Tonin PN, Serruya C, Sun CC, Narod SA and, Foulkes WD: Is hereditary site-specific ovarian cancer a distinct genetic condition? *Am J Med Genet***75**: 55-58, 1998.

5*. Hébert-Blouin M-H, Koufogianis V, Gillett P and Foulkes WD: Fallopian tube cancer in a *BRCA1* mutation carrier: rapid development and failure of screening. A*m J Obstet Gynecol* **186**: 53-4, 2002.

6*. Al-Saffar M and Foulkes WD: Hereditary ovarian cancer due to a non-ovarian cancer cluster region (OCCR) *BRCA2* mutation: Is the OCCR useful clinically? *J Med Genet* 39(11): e68, 2002.

7*. Ah Mew N, Hamel N, Galvez M, Al-Saffar M and Foulkes WD: Haplotype analysis of a *BRCA1*:185delAG mutation in a Chilean family supports its Ashkenazi origins. *Clin Genet* 62: 151-156, 2002

8. Kasprzak L, Mesurolle B, Tremblay F, Galvez M, Halwani F, Foulkes WD. Invasive breast cancer following bilateral subcutaneous mastectomy in a *BRCA2* mutation carrier: a case report and review of the literature. *World J Surg Oncol* 3:52, 2005.

h) Letters (new data or novel hypotheses, not necessarily peer-reviewed)

1*. Foulkes W, Goddard A and Patel K: Retinoblastoma linked with Seascale. *BMJ* **302**: 409, 1991.

2*. Foulkes W, Black DM, Solomon E and Trowsdale J: Allele loss on chromosome 17q in sporadic ovarian cancer. *Lancet* **338**: 444-445, 1991.

3. Foulkes W: Tumour suppressor genes in ovarian cancer. *BMJ* **307**: 1009, 1993.

4. Brunet J-S, Narod SA, Tonin P and Foulkes WD. *BRCA1* and ovarian cancer survival. *N Engl J Med* **336**:1256, 1997.

5*. Foulkes WD and Narod SA: Re: Family history of cancer and risk of lung cancer among lifetime non-smoking women in the United States. *Am J Epidemiol* **146**: 364, 1997.

6*. Foulkes WD, Wong N, Rozen F, Brunet, J-S and Narod SA: Breast cancer survival in *BRCA1* carriers. *Lancet* **351**: 1359, 1998.

7*. Yuan ZQ, Kasprzak L, Gordon PH, Pinsky L and Foulkes, WD: I1307K *APC* and *hMLH1* mutations in a non-Jewish family with hereditary non-polyposis colorectal cancer. *Clin Genet* **54**: 368-370, 1998.

8. Chappuis PO, Deschênes J and Foulkes WD. Long-term outcome of invasive breast cancer. *Lancet*, **355**: 1551, 2000.

9. Julian-Reynier C, Evans G, Foulkes W, Sobol H. International variation of women's decisions about prophylactic surgery. *Lancet* **356**: 1687, 2000

10*. Chappuis PO, Hamel N, Paradis A-J, Deschênes J, Tonin PN, Ghadirian P, Foulkes WD. Re: Population-based study of *BRCA1* and *BRCA2* mutations in 1035 unselected Finnish breast cancer patients. *J Natl Cancer Inst* **93**:152-153, 2001.

11*.Goffin JR, Chappuis PO, Wong N, Foulkes WD: Re: Magnetic Resonance Imaging and mammography in Women with a hereditary risk of breast cancer. *J Natl Cancer Inst* **93**:1754-5, 2001.

12. Andermann A, Thiffault I, Wong N, Gordon P, MacNamara E, Chong G, Foulkes W. Multimodal molecular screening is required to improve the sensitivity of MLH1 and MSH2 mutation analysis. *J Clin Oncol* **20**:1705-7, 2002.

13. Foulkes WD, Goffin J, Brunet J-S, Bégin LR, Wong N and Chappuis PO. Tamoxifen may be an effective treatment for BRCA1-related breast cancer irrespective of ER status. *J Natl Cancer Inst* **94**: 1504-1506, 2002.

14*. Cremin C, Wong N, Buzaglo K, Paradis A-J and Foulkes WD. Non-ovarian pelvic cancers in *BRCA1/2* mutation carriers and BRCAPRO statistical model. *J Clin Oncol* **20**: 3937-7, 2002.

15. Foulkes WD. Re: Potential for bias in studies on efficacy of prophylactic surgery for *BRCA1* and *BRCA2* mutation carriers. *J Natl Cancer Inst* **95**: 1344, 2003.

16. Foulkes WD. Re: Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. *J Natl Cancer Inst*; 96:1040-1, 2004.

17. Foulkes WD, Hamel N, Oros KK, Tonin PN. BRCA mutations and ductal carcinoma in situ. *JAMA* 294(5):553-4, 2005

i) Letters (commentary, not peer-reviewed)

1. Foulkes W: Breast cancer, desmoid tumours, and familial adenomatous polyposis. *Lancet* **342**: 1560-1561, 1993.

2. Foulkes W: The expanded role of NF1. *Nature Genet* **3**: 282, 1993.

3. Foulkes W: Detection of prostate cancer. *BMJ* **310**: 1139-40, 1995.

4*. Foulkes W, Glendon G and Narod S: Screening for ovarian cancer. *JAMA* **274**: 383, 1995.

5*. Rosenblatt DS, Foulkes WD and Narod SA: Genetic screening for breast cancer. *N Engl J Med* **334**: 1200, 1996.

6. Foulkes WD: Pitfalls of Genetic Testing. *N Engl J Med* **335**:1235-6, 1996.

7*. Foulkes WD and Narod SA: Ovarian cancer risk and family history. *Lancet* **349**: 878,

1997.

8. Foulkes WD: Survival in hereditary breast cancer. *Lancet* **350**: 366, 1997

9*. Foulkes WD, Wong N, Brunet J-S and Narod SA: *BRCA* mutations and survival in breast cancer. *J Clin Oncol* **16**: 3206-7, 1998

10. Chappuis PO, Narod SA and Foulkes WD: Screening for ovarian cancer. *Lancet* **354**: 509-510, 1999.

11. Sutton M, Laazari K and Foulkes WD: Response to "the traps and pitfalls inherent in the correlation of changes in the fibre diffraction pattern of hair with breast cancer". *Phys Med Biol* **48**: L11-L13, 2003.

12. Narasimhadevara R, Pollak MN and Foulkes WD. Re: Italian randomized trial among women with hysterectomy: tamoxifen and hormone-dependent breast cancer in high-risk women. *J Natl Cancer Inst* **95**: 917, 2003.

j) Technical reports

Foulkes WD. Ovarian cancer in Canada. Laboratory Centre for Disease Surveillance, Health Canada, 1998.

k) Selected abstracts (truncated at 2001)

1. Levi S, Beardshall K, Swift I, Foulkes W, Playford R, Ghosh P, Spencer J and Calam J: Camplylobacter pylori and duodenal ulcers: the gastrin connection. *Gut* **30**: A1443, 1989.

2. Ghosh P, Beardshall C, Playford RJ, Foulkes W, Levi S, Desa L, and Calam J: Gastrin releasing peptide (GRP) stimulated gastrin release falls after suppression of Helicobacter pylori in duodenal ulcer disease. *Gut*, **31**: A597, 1990.

3. Levi S, Goodlad RA, Stamp G, Lee C, Playford R, Ghosh P, Foulkes W, Wright NA and Hodgson HJF: The stomach and the duodenum of patients with arthritis respond to non-steroidal antiinflammatory drug administration by increasing cell turnover. *Gut*, **31**: A599, 1990.

4. Markie D, Foulkes W and Bodmer WF: Three probes recognise the same locus and form part of a linkage group on the long arm of chromosome six. Human Genome Mapping 11, *Cytogenet. Cell Genet.* **58**: nos. 3-4, 1914, 1991.

5. Foulkes W, Ozoa P, Campbell IG, Pignatelli M and Stamp G: Ovarian cancers show selected markedly positive staining with MOv18, an antibody that recognises a high affinity folate binding protein. *J. Pathol*., **167**: Suppl. 134A, 1991.

6. McFarlane CP, Foulkes WD, Gusterson BA and Spence RP: Characterisation of

*c-erb*B2 amplification and expression in ovarian tumour samples: evidence for a diagnostic genomic rearrangement. Presented at Annual AACR meeting, San Diego, California, May 1992.

7. Grant SG, Foulkes WD, Sieh W, Narod S and Bigbee WL: Elevated levels of bone marrow somatic mutation in long term cancer survivors. *Proc. Am. Assoc.Cancer Res.,* **36**: A151, 1995.

8. Foulkes WD, Brunet J-S, Kowalski LP, Franco EL and Narod SA: Family history is a risk factor for squamous carcinoma of the head and neck in Brazil: a case-control study. *Am. J Hum. Genet* **57S**: A63; 334, 1995

9. Sun S, Narod SA and Foulkes WD: A p16 mutation in a family with multiple cancers. *Eur. J. Hum. Genet*. 4 Suppl. 1: S11.003, 1996.

10. Foulkes WD, Brunet J-S, Sieh W, Black MJ, Shenouda G and Narod SA: Familial risks of squamous cell carcinoma of the head and neck. *Eur. J. Hum. Genet*. 4 Suppl. 1: 4.020, 1996.

11. Sun S, Narod SA, Jothy J, Kasprzak LZ and Foulkes WD: A p16 mutation in a family with multiple cancers**.** Genetique humaine au Quebec: Qui fait quoi? *Réseau de médecine génétique appliqués du FRSQ*. Abstract # 46.

12. Evans DGR, Kerr B, Foulkes W, Hadfield LD, Hopwood and Narod SA: Factitious breast cancer history: a new form of Munchausen syndrome. *Am. J. Hum. Genet*. **59S:** A66; 342, 1996.

13. Foulkes W, Flanders T, Lambert D, Narod S: Increased incidence of cancer in first-degree relatives of women with double primary cancers of the colorectum and endometrium. *Am. J. Hum. Genet.*, **59S:**A67; 347, 1996.

14. Bignell G, Sun S, Biggs P, Hamoudi R, Rosenblatt J, Buu P, Druker H, Hudson T, Houlston R, Narod SA, Stratton M and Foulkes W. Non-medullary thyroid cancer: attempts to locate susceptibility genes by linkage in two Canadian families with goitre and non-medullary thyroid cancer. *Am. J. Hum. Genet.* **59S**:A380; 2216, 1996.

15. Eeles RA, Dearnaley DP, Edwards SM, Badzioch M, Easton DF, Ardern-Jones A, Dowe A, Ford D, Shearer R, and 103 Collaborators (UK), Labrie F, Tonin P, Durocher F, Simard J, Narod SA and Foulkes W: The contribution of candidate genes to prostate cancer susceptibility. Presented at Winter British Prostate Group Meeting.

16. Provencher D, Godard B, Foulkes WD, Brunet J-S, Tonin PN, Mes-Masson, A-M, Droiun P, Dubuc-Lissoir J, Gauthier P, Audet-Lapointe P, Narod SA and Ghadirian P. Risk factors for familial and sporadic ovarian cancer among French-Canadians: a case-control study. Submitted to la societe des obstetricians et gynecologues du Canada, 1997 meeting.

17. Eeles R, Simard J, Teare D, Edwards S, Easton D, Dearnaley D, Durocher F, Shearer R, Ardern-Jones A, Dowe A, 105 Collaborators (UK), Narod S and Foulkes W. Does the hereditary prostate cancer gene, HPC1, contribute to a large proportion of familial prostate cancer? Published in *Br. J. Cancer* supplement, 1997.

18. Eeles RA, Durocher F, Simard J, Edwards SM, Badzioch M, Ford D, Dearnaley DP, Arden-Jones A, Dowe A, Shearer R, the CRC/BPG UK Familial Prostate Cancer Study Collaborators, Labrie F, Tonin PN, Easton DF, Narod SA, Foulkes WD. Analysis of the contribution of candidate genes to familial prostate cancer. *Br J Urol* 79: Suppl 1; 8-14.

19. Wong N, Brunet J-S, Narod SA, Bégin LR, Zhang JC, Martinez JJ, Tonin PN, Karp SE, Pollak MN, Foulkes WD: Germ-line *BRCA1* mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer. Presented at Terry Fox Workshop on Cancer Genetics, Canadian Collaboraive Group for Cancer Genetics, Toronto, May 31-June 1 1997. Abstract Poster #8.

20. Pal T, Flanders T, Narod SA, Foulkes W: Implications of Double primary cancers of the colon and endometrium.Presented at Terry Fox Workshop on Cancer Geneticss, Canadian Collaborative Group for Cancer Genetics, Toronto, May 31-June 1 1997. Abstract Poster #20.

21. Brunet J-S, Foulkes WD, Tonin P, Ghadirian P, Narod SA: Screening for Hereditary Breast cancer. Presented at Terry Fox Workshop on Cancer Geneticss, Canadian Collaborative Group for Cancer Genetics, Toronto, May 31-June 1 1997. Abstract Poster #5.

22. Eeles R, Durocher F, Edwards S, Teare D, Easton D, Dearnley D, Shearer R, Arden-Jones A, Dowe A, UK collaborators, Badzioch M, Amos C, Labrie F, Simard J, Narod S and Foulkes W. Does the hereditary prostate cancer gene, HPC1 contribute to a loarge proportion of famlial prostate cancer?-results from CRC/BPG UK, Texan and Canadian Consortium. Am J Hum Genet 61S: A64, 345, 1997

23. Wong N, Brunet J-S, Begin LR, Zhang JC, Martinez JJ, Tonin PN, Narod SA, Karp SE, Pollak MN and Foulkes WD. Germ-line BRCA1 mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer. Am J Hum Genet 61S: A89, 490, 1997

24. Bignell GR, Canzian F, Shayeghi M, Stark M, Shugart YY, Biggs P, Mangion J, Hamoudi R, Rosenblatt J, Buu P, Sun S, Stoffer SS, Goldgar DE, Romeo G, Houlston RS, Narod SA, Stratton MR and Foulkes WD: A familial non-toxic multinodular thyroid goiter locus maps to chromosome 14q but does not account for familial non-medullary thyroid cancer. Am J Hum Genet 61S: A268, 1561, 1997

25. Kasprzak L, Wong N, Ozaki J, Galvez M, Tonin PN, Rosenblatt DS and Foulkes WD: Ascertainment of familial cancers in McGill Hereditary Cancer Clinics. *Les Journees*

Genetiques' 98: *Réseau de médecine génétique appliqués du FRSQ*. Abstract # 105.

26. Tonin, PN, Mes-Masson A-M, Provencher D, Foulkes W, Morgan K, Narod S and Ghadirian P. Founder BRCA1 and BRCA2 mutations in French-Canadian breast and ovarian cancer families. *Les Journees Genetiques' 98*: *Réseau de médecine génétique appliqués du FRSQ*. Abstract #22

27. de Andrade M, Amos CI, Foulkes WD. Segregation analysis of squamous cell carcinoma of the head and neck: evidence for a major gene determining risk. Abstract #134, accepted for poster presentation at the seventh international genetic epidemiology society (IGES) meeting, Arcachon, France, Sept 11-12, 1998.

28. Foulkes WD Hamel N, Karimi S, Brunet J-S, Gilfix B, Ghadirian P, Narod SA and Black MJ: Increased risk of head and neck cancer in association with *GSTT1* nullizygosity for individuals with low exposure to tobacco and alcohol. Am J Hum Genet 63S: A20, 101, 1998

29. Wong N, Brunet J-S, Bégin LR, Vesprini D, Rozen F, Yuan ZQ, Abrahamson J, Karp E, Pollak M, Narod SA and Foulkes WD: Axillary node negative primary breast cancer in Ashkenazi Jewish *BRCA1* mutation carriers is associated with P53 over-expression and has a poor prognosis. Am J Hum Genet 63S: A47, 248, 1998

30. Dupuis L, Lerner B, Mecsas-Faxon S, Berlin B and Foulkes WD. The incidence of cancer in the first degree relatives of women diagnosed with endometrial cancer under the age of 55. Am J Hum Genet 63S: A67, 354, 1998.

31. May S, Yuan ZQ, McKinnon W, Lasko D, Greenblatt M, Gordon P, Pinsky L, Yandell D, Rousseau F and Foulkes W. How mutation analysis can link distantly-related families. Am J Hum Genet 63S: A78, 420, 1998.

32. International Consortium for Prostate Cancer Genetics (ICPCG). Meta-analysis of 1q24-25 linkage data in 780 prostate cancer families. American Urological Association, 1999.

33. Foulkes WD, Wong N, Brunet J-S, Vesprini D, Rozen F, Yuan, Pollak M, Narod SA, Trudel M and Bégin LR. Novel negative breast cancer in Ashkenazi Jewish women has a very good prognosis if the tumor is both HER2 and BRCA1 germ-line mutation negative. Reasons for Hope, National Scientific Conference, CBCRI, Toronto, Ontario, 17-19 June, 1999.

34. Yuan ZQ, Trifiro M, Wong N, Lasko D, Foulkes WD, Pinsky L, Khandjian E, Rousseau F, Gordon PH. Three novel germ-line mutations of hMLH1/hMSH2 in Montreal families with Hereditary Non-Polyposis Colorectal Cancer. Royal College of Physicians and Surgeons Annual Conference, Montreal, Sept 25, 1999, Abstract 0044.

35. Julian-Reynier CM, Evans G, Bouchard L, Eisinger F, Kerr B, Foulkes W, Blancquaert

I, Sobol H. Consultees' attitudes towards preventive strategies for Hereditary Breast Ovarian Cancer risk: Cultural differences between Manchester (UK), Marseilles (F) and Montreal (Ca). Am J Hum Genet 65S: A12, 58, 1999

36. Foulkes WD, Wong N, Brunet J-S, Trudel M, Paradis A-J, Kuperstein G, Chappuis PO, Kapusta L, Slingerland J, Narod SA and Bégin LR. Germ-line BRCA mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer: Survival disadvantage depends on nodal status. Am J Hum Genet 65S: A62, 322, 1999

37. Chappuis PO, Renard H, Kantemiroff T, Sanders K, MacMillan A, Black MJ, Goldgar DE and Foulkes WD. Increased incidence of thyroid cancer in the first degree relatives of probands with non-medullary thyroid cancer: a case-control-cohort study. Am J Hum Genet A121, 643, 1999

38. Kasprzak L, Nolet S, Gaboury L, Gregory W, Pavia C, Villabona C, Rivera-Fillat, Oriola J and Foulkes WD. Familial medullary thyroid carcinoma and prominent corneal nerves associated with a codon 804 germline mutation of the RET gene. Am J Hum Genet A132, 706, 1999

39. Foulkes WD, Satagopan JM, Chappuis PO, Wong N, Bégin LR, Boyd J, Offit K and Robson ME. The presence of a germ-line BRCA mutation is an independent poor prognostic marker in breast cancer: a two-center historical cohort study. Am J Hum Genet A105, 379, 2000

40. Robson ME, Roberge D, Chappuis PO, Offit K and Foulkes WD. Risk of Ipsilateral Recurrence (IBTR) and Metachronous Contralateral Breast Cancer (CBC) after Breast Conservation Therapy (BCT) in Women with Germline *BRCA1* or *BRCA2* Mutations. Slide presentation at the 23rd Annual San Antonio Breast Cancer Symposium. Presented in General Session IV, December 8, 2000.

41. Roberge D, Foulkes W, Wong N, Chappuis P, Bégin L, Chow T. Résultats de la mastectomie partielle suivie de radiothérapie chez les porteuses de gènes *BRCA1/BRCA2* mutants: implications thérapeutiques. Oral communication, 11e congrès national de la société française de radiothérapie oncologique, Paris, 23-24 novembre 2000. Cancer Radiothérapie 4: 1s 10s, 2000.

42. Canil CM, Markin G, Chappuis P, Goshen R, Meschino W, Goss P, Narod S, Foulkes W, Warner E. Comparison of clinical, radiological and pathological features in age-matched Ashkenazi Jewish (AJ) women with breast cancer with and without BRCA1 and BRCA2 mutations. Am Soc Clin Oncol A1649, 2001.

k) Others

Cervical cancer screening:

Foulkes W: The health of the nation. *Br. Med. J*. **303**: 311-312, 1991.

Conference report:
Foulkes W: Genetics of Cancer. *Lancet* **340**: 1402-1403, 1992.

Castration and Sex:
Foulkes W: Male and female castration. *Br. Med. J*. **308**:416, 1994.

Authorship criteria:
Foulkes WD and Neylon N: Redefining authorship. *Br. Med. J*. **312**: 1423, 1996.

Book review:
Foulkes W. *Hidden Histories of Science* Edited by Robert B Silvers. New York Review Books. *Br. Med. J.* **311**:1101, 1995.

JOURNAL REFEREE

***Ad hoc*-more than 10 reviews**
Journal of Medical Genetics
International Journal of Cancer
British Journal of Cancer

Between 5 and 10 reviews
Nature Genetics
Lancet
Journal of the National Cancer Institute
Cancer Research
Clinical Cancer Research
European Journal of Cancer

Between 1 and 5 reviews
American Journal of Human Genetics
Lancet Oncology
Human Mutation
Oncogene
Gastroenterology
Prostate
Journal of Clinical Pathology
Oncology Research
Molecular and Cellular Probes
Canadian Journal of Oncology

BOOK REFEREE

Cambridge University Press

THESIS DEFENCE/REFEREE/COMMITTEE

PhD, McGill Dept. Biology
Ronald Lafreniere, June 17, 1997.

Ph.D, McGill Dept Biology
Adriana Diaz Anzaluda,
April 1999-current

PhD, McGill Dept Oncology
David Hamilton
May 2000-current

MSc, McGill Dept. Epidemiology and Statistics
Hela Makni, April 2000

MSc, McGill Dept. Biology
Sahar Sibani, January 2001

MSc, McGill Dept. Human Genetics
Andrea Karin Lawrance
May 2001-current

INVITED TALKS and SEMINARS, 1995-2006

Scientific Audience

a) International

September 19, 1995
Title:*Increased risk of squamous cell carcinoma of the head and neck in association with a family history of this cancer.*
Vermont Cancer Center
Burlington, Vermont

May 9, 1996
Title: *Genetics of head and neck cancer*
Epidemiology of head and neck cancer meeting
IARC, Lyon, France

December 9, 1996
Title: *Resolving uncertainty in hereditary breast and ovarian cancer*
Beatson Institute for Cancer Research
Glasgow, Scotland

December 10, 1996
Title: *Developing a Cancer Genetics Service*
Department of Medical Genetics, University of Glasgow,
Yorkhill Hospital
Glasgow, Scotland

February 13, 1998
Title: *Epidemiological and clinical studies of cancer genetics in the Ashkenazi Jewish population.*
Department of Human Genetics Seminar
Schwartz Building, Memorial Sloan-Kettering Cancer Center,
New York, New York.

March 12, 1998
Title: *The genetics of breast cancer in the Ashkenazi Jewish population*
Department of Epidemiology,
MD Anderson Cancer Center,
Houston, Texas.

March 12, 1998
Title: *Familial multinodular goitre and hereditary non-medullary thyroid cancer*
Department of Endocrinology,
MD Anderson Cancer Center,
Houston, Texas.

May 1, 1998
Title: *Endocrine cancers*
Department of Human Genetics
A "genetics of human cancer" course lecture
Memorial Sloan-Kettering Cancer Center,
New York, New York.

September 15, 1998
Title: *Overview of studies of prognosis in familial and hereditary breast cancer*
Breast Cancer Linkage Consortium,
Dublin, Ireland.

September 17, 1998
Title: *Genetics of Breast Cancer*
Division of Investigative Sciences,
Imperial College of Science and Medicine,
Hammersmith Hospital, London

September 18, 1998
Title: *Cancer Genetics: Much Ado about Nothing?*

GlaxoWellcome Medicines Research Centre,
Gunnels Wood Lane
Stevenage, Herts, UK.

October 5, 1998
Title: *Research in progress*
Vermont Cancer Center retreat,
Baldwin's Creek,
Bristol,VT, USA

May 26, 1999
Title: *The influence of familial and hereditary factors on the clinicopathological features and prognosis of breast cancer*
Department of Epidemiology
Fred Hutchinson Cancer Research Center
Seattle, WA, USA

September 2, 1999
Title: *Recent advances in cancer genetics*
Division of Genetic Medicine, Department of Medicine,
Vanderbilt University
Nashville, TN, USA.

December 3, 1999
Title: C*linicopathological features and prognosis of hereditary breast cancer*
Netherlands Cancer Institute
Antoni van Leeuwenhoek Huis,
Amsterdam, Netherlands

December 16, 1999
Title: C*linical, Pathological and Survival studies in hereditary breast cancer*
Duke University Medical Center
Duke University
North Carolina, USA

September 25, 2000
Title: Hereditary breast cancer: genes, risks and outcome
University of Newcastle Medical School
University of Newcastle,
Northumberland, UK

November 28, 2001
Title: Clinicopathological studies of hereditary breast cancer
CHUV,
University of Lausanne
Lausanne, Switzerland

March 27, 2003
Title: Founder populations and cancer genetics: a view from just north of here
NHGRI, Division of Intramural Research Seminar Series,
NIH,
Bethesda, MD, USA

September 22, 2003
Title: *Clinico-pathological features of BRCA1-related breast cancer*
Division of Medical and Molecular Genetics
Guy's Hospital,
London, UK

September 23, 2003
Title: *Five things I learnt about BRCA1-related breast cancer in the last year*
Gjesteforelesning,
Gades Institute,
Haukeland University Hospital
Bergen, Norway

September 24, 2003
Title: *Five things I learnt about BRCA1-related breast cancer in the last year*
Netherlands Cancer Institute
Amsterdam, Netherlands

February 2, 2006
Title: *Genetic Risk Assessment*
5th International "From Gene to Cure" Congress
Vrije Universiteit Amsterdam
Amsterdam, Netherlands

February 2, 2006
Title: *Prevention of Hereditary Breast Cancer*
5th International "From Gene to Cure" Congress
Vrije Universiteit Amsterdam
Amsterdam, Netherlands

April 20, 2006
Title: *Clinico-pathological features of basal-like/BRCA1 tumors*
"Basal-like and BRCA1-associated Breast Cancer" meeting
Harvard Club
Boston, MA, USA

August 16, 2006
Title: *Recent advances in understanding of the inherited susceptibility to cancers of the prostate, pancreas, stomach and colorectum*

Australian Ovarian Cancer Study and the Family Cancer Clinics of Australia
Couran Cove Island Resort
Stradbroke Island, Australia

August 18, 2006
Title: *Hereditary breast cancer: from pathology to treatment and beyond*
Australian Ovarian Cancer Study and the Family Cancer Clinics of Australia
Couran Cove Island Resort
Stradbroke Island, Australia

October 28, 2006
Title: Breakthrough treatments for BRCA1 and BRCA2 mutation carriers
10th Annual Cincinnati Comprehensive Breast Cancer Conference
Cutting Edge Strategies in Breast Cancer: The next decade
Cincinnati, OH, USA

November 9, 2006
Title: Hereditary breast cancer: from pathology to treatment and beyond
Cancer Colloquia IV: Cell and Molecular Biology of Breast Cancer
University of St-Andrews
St-Andrews, Scotland

b) National

April 26, 1996
Title: *Genetics of head and neck cancer*
Cancer Genetic Epidemiology Workshop
Environmental Health Centre
Ottawa, Ontario

February 24, 1999
Title: *Genetics of Breast Cancer: some observations from the study of founder populations in Quebec*
Division of Cancer Biology Research Seminar,
Sunnybrook and Women's College Hospital Health Sciences Centre,
Toronto, ON, Canada

May 19, 1999
Title: *Genetics of Breast and Ovarian Cancer*
"New Developments in prenatal diagnosis and medical genetics"
University of Toronto CME course
Toronto, ON, Canada

June 20, 1999
Title: *Node negative breast cancer in Ashkenazi Jewish women has a very good prognosis if the tumor is both HER2 and BRCA1 germ-line mutation negative*

Reasons for Hope: NCIC/CBCRI conference
Toronto, ON, Canada

June 21, 2001
Title: *Treatment issues in hereditary breast cancer*
Theme: The genetic basis of disease
Canadian Federation of Biological Societies, 44th annual meeting.
Ottawa Congress Centre
Ottawa, ON, Canada

October 7, 2004
Title: *Exons, Introns, Enhancers, Deletions and Founders: an overview of HNPCC in Quebec*
Oncogenetics: Achievements and Challenges,
17ieme entretiens du Centre Jacques Cartier
Crowne Plaza Hotel, Montreal, Quebec

June 15, 2006
Title: *Genetics and Breast Cancer: An update*
Toronto Breast Cancer Symposium 2006
Metro Toronto Convention Center, Toronto, Ontario

c) Local/Provincial

September 28, 1995
Title: *Familial Risks of Squamous Cell Carcinoma of the Head and Neck*
Annual Meeting of Quebec ORL Society
Montibello, Quebec

March 26, 1996
Title: *p16 and Familial Cancer*
Institut de Cancer de Montreal - Hopital Notre Dame
Montreal, Quebec

June 19, 1996
Title: *A p16 mutation in a family with multiple cancers*
Les Journées de Génétique Humaine - Réseau de Médicine Génétique Appliqués du FRSQ
Montreal, Quebec

October 24, 1997
Title: *A gene for familial multinodular goitre maps to chromosome 14q*
Annual Congress of the Quebec ORL Association,
Chateau Frontenac,
Quebec City, Quebec

November 20, 1997
Title: *The genetics of breast cancer*

Annual Scientific Meeting of Clinical Biochemists of Quebec,
Hotel Vogue,
Montreal, Quebec

May 29, 1999
Title: *Hereditary predisposition to breast and ovarian cancer*
Annual Congress of the Quebec Obstetrics and Gynecology Association (AOGQ)
Hotel Delta Sherbrooke,
Sherbrooke, Quebec

September 20, 2002
Title: *Genetic testing for colorectal cancer*
3rd Annual Montreal Colon and GI cancers conference
Queen Elizabeth Hotel
Montreal, Quebec

October 24, 2002
Title: *Genetics of Skin Cancer*
247th Scientific meeting of the Montreal Dermatological Society
Royal Victoria Hospital
Montreal, Quebec

October 4, 2002
Title: *Screening or Risk Reduction?*
1st International Cancer Prevention Symposium-Chagnon Foundation
Ritz Carlton Hotel,
Montreal, Quebec

November 13, 2002
Title: *Genetics of Breast Cancer*
Cité de la Santé Hematology/Oncology Group
Laval, Quebec

June 25, 2004
Title: *Screening of High Risk Patients*
23rd International Congress of Radiology of the International Society of Radiology
Palais des Congrès, Montreal, Quebec

October 7, 2004
Title: Exons*, Introns, Enhancers, Deletions and Founders: an overview of HNPCC in Quebec*
Oncogenetics: Achievements and Challenges,
17ieme entretiens du Centre Jacques Cartier
Crowne Plaza Hotel, Montreal, Quebec

November 25, 2004
Title: *Survol sur la génétique et la prise en charge du cancer colorectal héréditaire*

Centre intégré de lutte contre le cancer de la Montérégie, Réseau Cancer Montérégie
Hôtel Gouverneur Île Charron, 2405 Île Charron,
Longueuil, Quebec

December 15, 2004
Title: *Genetic diseases in the adult: New opportunities*
Hôtel Vogue, Montreal, Quebec

September 28, 2005
Title: *Genetics of colorectal cancer: What's new?*
CCMG 2005 Annual Meeting
Château Bromont
Bromont, Quebec

October 12, 2005
Title: *Genetic influence of breast and gynecological cancers in pre-menopausal women*
10th McGill International Symposium on Reproductive Endocrinology & Infertility and Women's Health
Centre Mont-Royal, Montreal, Quebec

October 20, 2005
Title: *Overview - 10 years of BRCA1 and BRCA2*
BRCA: Today & Tomorrow
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes
Marriott Château Champlain, Montreal, Quebec

October 20, 2005
Title: *Outcome following BRCA1/2 related breast cancer*
BRCA: Today & Tomorrow
First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes
Marriott Château Champlain, Montreal, Quebec

d) Institutional

January 11, 1996
Title: *Breast Cancer Syndromes*
Endocrinology Research Seminar - Royal Victoria Hospital
Montreal, Quebec

February 28, 1996
Title: *Familial Breast Cancer*
Oncology Rounds - Royal Victoria Hospital
Montreal, Quebec

February 29, 1996
Title: *Preventive Surgery and the High-risk Patient*
Surgical Grand Rounds - Royal Victoria Hospital
Montreal , Quebec

March 29, 1996
Title: *Germline mutations in p16 and the risk of cancer*
McGill Genetics rounds: Case presentations-Royal Victoria Hospital
Montreal, Quebec

November 8, 1996
Title: *Controversies Surrounding New Genetic Testing* (Panel Discussion)
47th McGill University Annual Refresher Course for Family Physicians
Montreal, Quebec

November 14, 1996
Title: *The role of Preventive Surgery in the High-risk Individual*
Surgical Grand Rounds - Sir M.B. Davis Jewish General Hospital
Montreal , Quebec

November 22, 1996
Title: *Resolving uncertainty in hereditary breast and ovarian cancer*
McGill Genetics Rounds - Montreal Children's Hospital
Montreal, Quebec

November 25, 1996
Title: *Familial Cancer* (with Dr. Patricia Tonin)
Grand Medical Rounds - Sir M.B. Davis Jewish General Hospital
Montreal, Quebec

February 20, 1997
Title: *Genetics and epidemiology of non-medullary thyroid cancer*
Endocrinology rounds,
Montreal General Hospital
Montreal, Quebec.

March 20, 1997
Title: *Methods and recent results in the genetics of cancer susceptibility*
Montreal Cancer Research Group,
McGill Cancer Centre,
Montreal, Quebec.

November 13, 1997
Title: *The genetics of breast cancer*
Department of Epidemiology and Biostatistics,
Fall Seminar Series,

McGill University, Montreal

November 24, 1997
Title: *Female cancer and genetics*
Department of Obstetrics and Gynaecology Grand Rounds
Primrose Amphitheatre, Royal Victoria Hospital,
Montreal, Quebec.

December 5, 1997
Title: *Female cancers and genetics*
Department of Obstetrics and Gynaecology Grand Rounds
Block Amphitheatre, SMBD-Jewish General Hospital,
Montreal, Quebec.

December 10, 1997
Title: *Recent advances in cancer genetics*
Department of Medicine Grand Rounds
JSL Browne Amphitheatre, Royal Victoria Hospital,
Montreal, Quebec.

December 15, 1997
Title: *Breast cancer: endocrine and genetic factors* (with Professors M. Pollak and L. Pinsky)
Department of Medicine Grand Rounds
Block Amphitheatre, SMBD-Jewish General Hospital,
Montreal, Quebec.

February 5, 1998
Title: *Genetics of breast and colorectal cancer*
Department of Surgery Grand Rounds
Osler Amphitheatre, Montreal General Hospital,
Montreal, Quebec.

February 17, 1998
Title: *Cancer genetics: an introduction*
Department of Medicine Grand Rounds
Osler Amphitheatre, Montreal General Hospital,
Montreal, Quebec.

April 24, 1999
Title: *Hereditary ovarian cancer*
4th McGill International Symposium on reproductive endocrinology and infertility
Jeanne Timmins Amphitheatre,
McGill University, Montreal.

May 12, 1999
Title: *Recent advances in breast and ovarian cancer genetics*

Surgical Grand Rounds,
Royal Victoria Hospital,
McGill University, Montreal

August 25, 1999
Title: *The role of BRCA1 and BRCA2 in breast and ovarian cancer*
Obstetrics and Gynecology Rounds
Royal Victoria Hospital,
McGill University, Montreal

December 13, 1999
Title: *Genetics and Adult Onset diseases: A changing role for medical genetics*. (with Prof. D. Rosenblatt)
Medical Grand Rounds,
Sir M.B. Davis-Jewish General Hospital,
McGill University, Montreal

January 12, 2000
Title: *Genetic predisposition and outcome from cancer*
Montreal Cancer Research Group,
McGill Cancer Centre,
Montreal, Quebec.

February 24, 2000
Title: *Non-medullary thyroid cancer*
Endocrinology Grand Rounds
Sir MB Davis-Jewish General Hospital
Montreal, Quebec.

March 15, 2000 (with Ms. Lidia Kasprzak and Dr. Georges Chong)
Title: *Genetics and Cancer: How mutation analysis affects clinical management*
Medical Grand Rounds
Royal Victoria Hospital
MUHC, Montreal, Quebec

April 4, 2000 (with Ms. Lidia Kasprzak)
Title: *Colorectal Cancer Genetics: How mutation analysis affects clinical management*
Medical Grand Rounds
Montreal General Hospital
MUHC, Montreal, Quebec

November 7, 2000
Title: *Management of Hereditary Breast and Ovarian Cancer*
Medical Grand Rounds
Montreal General Hospital
MUHC, Montreal, Quebec

November 8, 2000
Title: *Management of Hereditary Breast and Ovarian Cancer*
Medical Grand Rounds
Royal Victoria Hospital
MUHC, Montreal, Quebec

October 22, 2001
Title: *Management of Hereditary Breast and Ovarian Cancer: Prevention, Early Detection and Treatment*
Medical Grand Rounds
Sir M.B. Davis-Jewish General Hospital,
McGill University, Montreal

November 17, 2001
Title: *McGill Program in Cancer Genetics: Bringing together human genetics and oncology*
McGill Oncology Research Retreat,
November 16-17,
Hotel Days Inn,
Montreal

December 16, 2002
Title: *Genetics of Cancer: an update*
MUHC Radiation Oncology Group
Montreal General Hospital

November 23, 2004
Title: *Clinicopathological features of Hereditary Breast Cancer: Ten years on*
MUHC Clinical and Research Seminar
Meakins Auditorium
McIntyre Building
McGill University

December 15, 2004
Title: *Genetics of Colorectal cancer*
GI residents
Montreal General Hospital

Lectures to Interested Groups and/or the General Public

October 26, 1996
Title: *Risk factors, prevention and early diagnosis in prostate cancer*
First Patient Advocates for Advanced Cancer Treatment (PAACT) Prostate Cancer Conference,
Grand Rapids, MI, USA

May 22, 2001
Title: *Genetics and Cancer: Prevention, Early Diagnosis and Treatment*
Research Governor's Society First Lecture Series
Lady Davis Institute for Medical Research,
Montreal, Quebec.

October 24, 2001
Title: *Genetic Testing for Cancer Susceptibility*
38th Annual André Aisenstadt Clinical Day
The Use of Genetic tests in Medical Diagnosis and Treatment
Sir M.B. Davis-Jewish General Hospital,
McGill University, Montreal

September 18, 2002
Title: *Genetic testing for colorectal cancer*
3rd Annual Montreal Colon and GI cancers pre-conference lay workshop
Queen Elizabeth Hotel
Montreal, Quebec

October 1, 2002
Title: *Genetics of Breast Cancer*
CanSupport Public Lecture
Omni Hotel,
Montreal, Quebec

September 27, 2004
Title: *The Why, Where and How of genes and diseases in the Jewish population*
National Council of Jewish Women of Canada
The power of genealogy
Gelber Conference Center Montreal, Quebec

September 19, 2005
Title: *Role of genetic factors in cancer & familial diseases*
National Council of Jewish Women of Canada
Gelber Conference Centre
Montreal, Quebec

Am. J. Hum. Genet. 77:219–229, 2005

A Combined Genomewide Linkage Scan of 1,233 Families for Prostate Cancer–Susceptibility Genes Conducted by the International Consortium for Prostate Cancer Genetics

Jianfeng Xu,[1] Latchezar Dimitrov,[1] Bao-Li Chang,[1] Tamara S. Adams,[1] Aubrey R. Turner,[1] Deborah A. Meyers,[1] Rosalind A. Eeles,[2] Douglas F. Easton,[2] William D. Foulkes,[2] Jacques Simard,[2] Graham G. Giles,[2] John L. Hopper,[2] Lovise Mahle,[2] Pal Moller,[2] Tim Bishop,[2] Chris Evans,[2] Steve Edwards,[2] Julia Meitz,[2] Sarah Bullock,[2] Questa Hope,[2] The ACTANE Consortium,[2] Chih-lin Hsieh,[3] Jerry Halpern,[3] Raymond N. Balise,[3] Ingrid Oakley-Girvan,[3] Alice S. Whittemore,[3] Charles M. Ewing,[4] Marta Gielzak,[4] Sarah D. Isaacs,[4] Patrick C. Walsh,[4] Kathleen E. Wiley,[4] William B. Isaacs,[4] Stephen N. Thibodeau,[5] Shannon K. McDonnell,[5] Julie M. Cunningham,[5] Katherine E. Zarfas,[5] Scott Hebbring,[5] Daniel J. Schaid,[5] Danielle M. Friedrichsen,[6] Kerry Deutsch,[6] Suzanne Kolb,[6] Michael Badzioch,[2,6] Gail P. Jarvik,[6] Marta Janer,[6] Leroy Hood,[6] Elaine A. Ostrander,[6] Janet L. Stanford,[6] Ethan M. Lange,[7] Jennifer L. Beebe-Dimmer,[7] Caroline E. Mohai,[7] Kathleen A. Cooney,[7] Tarja Ikonen,[8] Agnes Baffoe-Bonnie,[8] Henna Fredriksson,[8] Mika P. Matikainen,[8] Teuvo LJ Tammela,[8] Joan Bailey-Wilson,[8] Johanna Schleutker,[8] Christiane Maier,[9] Kathleen Herkommer,[9] Josef J. Hoegel,[9] Walther Vogel,[9] Thomas Paiss,[9] Fredrik Wiklund,[10] Monica Emanuelsson,[10] Elisabeth Stenman,[10] Björn-Anders Jonsson,[10] Henrik Grönberg,[10] Nicola J. Camp,[11] James Farnham,[11] Lisa A. Cannon-Albright,[11] and Daniela Seminara[12,*]

[1]Data Coordinating Center, [2]ACTANE, [3]BC/CA/HI, [4]Johns Hopkins University, [5]Mayo Clinic, [6]PROGRESS, [7]University of Michigan, [8]University of Tampere and Tampere University Hospital, [9]University of Ulm, [10]University of Umeå, [11]University of Utah, and [12]National Cancer Institute

Evidence of the existence of major prostate cancer (PC)–susceptibility genes has been provided by multiple segregation analyses. Although genomewide screens have been performed in over a dozen independent studies, few chromosomal regions have been consistently identified as regions of interest. One of the major difficulties is genetic heterogeneity, possibly due to multiple, incompletely penetrant PC-susceptibility genes. In this study, we explored two approaches to overcome this difficulty, in an analysis of a large number of families with PC in the International Consortium for Prostate Cancer Genetics (ICPCG). One approach was to combine linkage data from a total of 1,233 families to increase the statistical power for detecting linkage. Using parametric (dominant and recessive) and nonparametric analyses, we identified five regions with "suggestive" linkage (LOD score >1.86): 5q12, 8p21, 15q11, 17q21, and 22q12. The second approach was to focus on subsets of families that are more likely to segregate highly penetrant mutations, including families with large numbers of affected individuals or early age at diagnosis. Stronger evidence of linkage in several regions was identified, including a "significant" linkage at 22q12, with a LOD score of 3.57, and five suggestive linkages (1q25, 8q13, 13q14, 16p13, and 17q21) in 269 families with at least five affected members. In addition, four additional suggestive linkages (3p24, 5q35, 11q22, and Xq12) were found in 606 families with mean age at diagnosis of ≤65 years. Although it is difficult to determine the true statistical significance of these findings, a conservative interpretation of these results would be that if major PC-susceptibility genes do exist, they are most likely located in the regions generating suggestive or significant linkage signals in this large study.

Received March 22, 2005; accepted for publication May 27, 2005; electronically published June 29, 2005.

Address for correspondence and reprints: Dr. William B. Isaacs, Marburg 115, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287. E-mail: wisaacs@jhmi.edu

* The authors' affiliations can be found in the Acknowledgments.

0002-9297/2005/7702-0005$15.00

Introduction

Familial clustering of prostate cancer (PC [MIM 176807]) has been consistently recognized for many years (reviewed by Isaacs and Xu [2002]). Segregation analyses and twin studies strongly suggest that genetic factors ex-

plain at least some of the familial aggregation of PC (reviewed by Schaid [2004]). Research groups worldwide have recruited families with multiple members with PC and have performed linkage analyses to search for PC-susceptibility genes. More than a dozen genomewide screens have been performed (Easton et al. 2003), and numerous regions have been suggested as harboring hereditary PC (HPC) genes. Furthermore, several genes in regions linked to PC have been proposed as candidate HPC genes, notably *ELAC2* (MIM 605367), *RNASEL* (MIM 180435), and *MSR1* (MIM 153622) (Tavtigian et al. 2001; Carpten et al. 2002; Xu et al. 2002).

Despite these extensive efforts, linkage findings suggested by individual groups and proposed associations with variants in candidate genes have not been reproducibly replicated by other groups. The difficulties in mapping PC genes have been widely discussed (Isaacs and Xu 2002; Edwards and Eeles 2004; Ostrander et al. 2004; Schaid 2004). Briefly, it is likely that multiple genes predispose to PC and that no single gene is sufficiently important to provide a reliable linkage signal when a small number of families are analyzed. PC linkage may be further complicated by phenocopies, particularly given the high prevalence of the disease and widespread use of prostate-specific antigen screening. These difficulties are inherent to PC-linkage studies, and, although they cannot be completely overcome, several approaches can be used to reduce their impact. One approach is to study a much larger number of families, which should improve the statistical power to detect regions containing genes that are mutated in a small proportion of families. Another approach is to study subsets of families with PC that are more likely both to segregate mutations in genes conferring a strong PC risk and to have a reduced number of phenocopies, such as those with a large number of affected members and/or affected members with early ages at diagnosis.

The International Consortium for Prostate Cancer Genetics (ICPCG) was formed to facilitate the task of PC–susceptibility gene identification through the combined analyses of linkage data from families with PC. In the present study, we describe the results from a combined genomewide screen for PC-susceptibility genes among 1,233 PC-affected families within the ICPCG, the largest study of its kind to date.

Methods

Ascertainment of Families

The overall ICPCG study population was described in detail elsewhere (Schaid et al. 2005). All members of the ICPCG recruited their study population, supported through their own research funding. Ten ICPCG groups participated in this combined genomewide screen, ACTANE (Anglo/Canadian/Texan/Australian/Norwegian/European Union Biomed), BC/CA/HI (British Columbia, California, and Hawaii), Johns Hopkins University (JHU), Mayo Clinic, University of Michigan, PROGRESS (Prostate Cancer Genetic Research Study, Fred Hutchinson Cancer Research Center), University of Tampere in Finland, University of Ulm in Germany, University of Umeå in Sweden, and University of Utah. There were 1,233 PC pedigrees in this combined analysis. The research protocols and informed consent procedures were approved by each group's institutional review board.

Definition of Affection Status and Classification of Pedigrees

Affected individuals were defined as "those men affected with PC who had been confirmed by either medical records or death certificates." Affected individuals without either medical records or death-certificate confirmation were considered as having unknown affection status (hence, instances of self-reported PC and of PC status that was based solely on family-history interviews were considered of unknown status). Because of this restricted definition, some pedigrees had fewer affected men than were previously reported in publications by the respective groups. All men without a diagnosis of PC were coded as having unknown affection status, regardless of whether they had undergone screening for PC. Hence, all analyses were based on the sharing of marker genotypes among affected individuals, with no consideration of the phenotype for the remaining subjects. Although such an approach may result in some loss of power, it provided a uniform approach across all participating groups.

Genotyping and Consensus Genetic Map

Various methods were used by different groups to genotype microsatellite markers in their respective genomewide screen, as described in detail elsewhere (Hsieh et al. 2001; Cunningham et al. 2003; International ACTANE Consortium 2003; Janer et al. 2003; Lange et al. 2003; Schleutker et al. 2003; Wiklund et al. 2003, Xu et al. 2003; Maier et al. 2005; Camp et al., in press). Different sets of genomewide-screen markers were used by these 10 groups (see individual references for complete description of markers), with a range of information contents of 0.38–0.57 across the various groups and a total of 1,322 markers. To facilitate a combined linkage analysis, we generated a consensus map by aligning all these markers to the draft human reference sequence (physical position) on the basis of the Human hg13 assembly (released November 14, 2002). Ten of these markers could not be uniquely located in the human reference sequence and were dropped from the combined analysis. The genetic position of the aligned markers was pri-

marily determined on the basis of the deCode map (Kong et al. 2002). Among the 1,312 mapped markers, we were able to find the deCode genetic position for 964 markers. For the remaining 348 markers, for which only physical position was available, we estimated their genetic positions by interpolation based on the flanking markers for which both physical positions and deCode positions are available.

Linkage-Analysis Methods

The combined linkage analysis was performed in two stages. In the first stage, the linkage analyses were performed by each of the 10 groups, by use of the same definition of affection status and parametric model and the same linkage programs and options. All linkage results were based on multipoint calculations implemented in the Genehunter-Plus software (Kruglyak et al. 1996; Kong and Cox 1997). Because of their large size, the Utah pedigrees were selected from the larger set of all Utah pedigrees with at least four subjects with PC with no more than two meioses separating them (Camp et al. 2005); these pedigrees were then further trimmed to allow analysis by Genehunter-Plus. The analysis performed by each group was implemented by scripts provided by the ICPCG Data Coordinating Center (DCC), to facilitate consistency and automation. Although different genomewide screen markers were used among groups, the marker position was determined on the basis of the consensus map described above; therefore, the length of each chromosome was the same across all the groups. The linkage was evaluated at a resolution of 1 cM for each chromosome. The output files containing pedigree-specific linkage information at every cM across the genome were sent to the DCC. In the second stage, a combined analysis was performed at the DCC. For nonparametric linkage analysis, the combined allele-sharing LOD score was evaluated for each chromosome on the basis of the family-specific allele sharing at each centimorgan by use of the computer program ASM (Kong and Cox 1997). For the parametric linkage analysis, the combined LOD score with the assumption of heterogeneity (HLOD) was evaluated for each chromosome, on the basis of the family-specific LOD score at each centimorgan, by use of the computer program HOMOG (Ott 1999). Throughout the present study, we used LOD scores to describe HLODs for the results of parametric analyses and allele sharing LODs for nonparametric analyses.

The allele frequencies used were population specific; that is, for each marker, allele frequencies were estimated by counting alleles across all families within each individual group, without consideration of genetic relationships. Although not fully efficient, this provides straightforward, unbiased allele-frequency estimates. Because few families within any participating group had a known nonwhite racial background, allele frequencies were estimated from the pool of all data within a group, without consideration of race. Both nonparametric and parametric linkage analyses were performed. Allele-sharing nonparametric linkage analysis was performed, because that did not require specification of a model and would be expected to have good power against a wide range of alternative models. The linear allele-sharing model was implemented using ASM (Kong and Cox 1997). Families were weighted equally, and the score function "all" was used, which provides more evidence of linkage than does the "pairs" option whenever most affected individuals in a pedigree share the same allele that is identical by descent. For the parametric linkage analyses, a dominant model and a recessive model were used. The dominant

Table 1

Characteristics of Families

ICPCG Member	Mean Age at Diagnosis[a] (years)		No. of Affected Members				Race[b]		Total No. of Families
	≤65	>65	2	3	4	≥5	White	Black	
ACTANE	41	21	18	32	11	3	64	0	64
BC/CA/HI	41	57	24	54	16	4	83	7	98
JHU	95	93	2	26	47	113	169	17	188
Mayo Clinic	72	87	70	58	21	10	158	0	159
PROGRESS	141	113	38	107	66	43	240	8	254
University of Michigan	103	73	55	76	29	16	158	16	176
University of Tampere	3	7	0	2	5	3	10	0	10
University of Ulm	84	55	60	42	29	8	139	0	139
University of Umeå	10	40	0	13	17	20	50	0	50
University of Utah	16	79	18	14	14	49	95	0	95
Total	606	625	285	424	255	269	1,166	48	1,233

[a] Information about family mean age at diagnosis was not available for two families.
[b] Nineteen families are from other ethnic groups, such as Asian, Hispanic, or Native American.

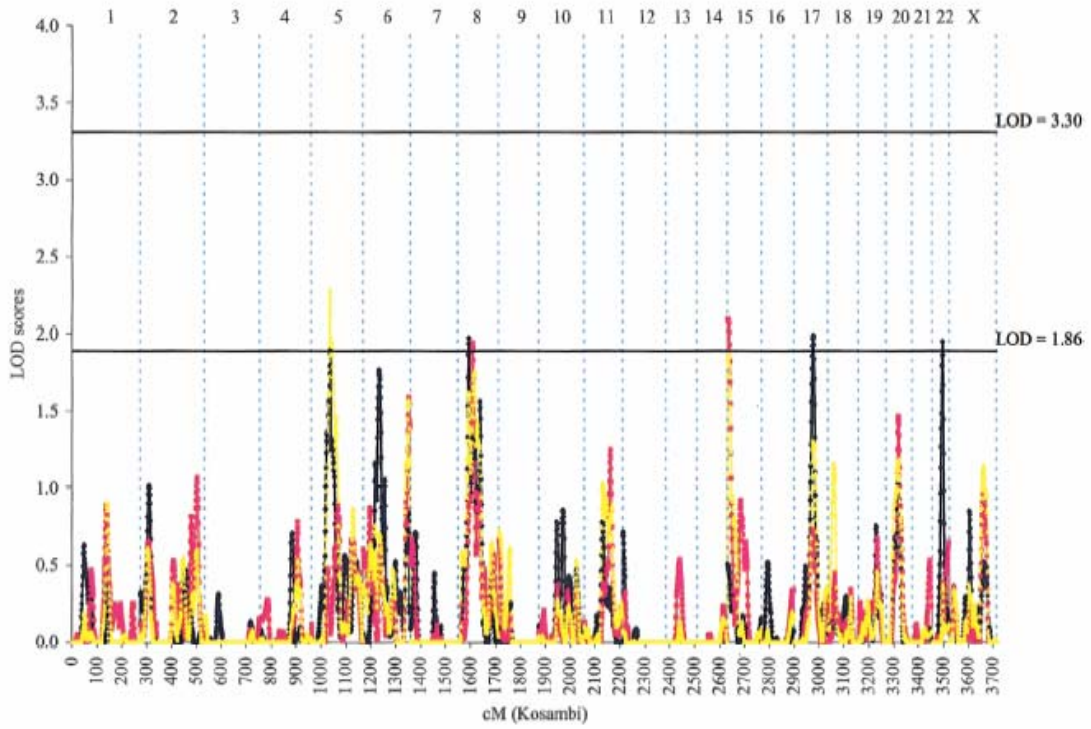

Figure 1 Combined genomewide screen for PC-susceptibility genes with use of nonparametric and parametric multipoint linkage analyses among the entire set of 1,233 PC-affected families recruited from 10 ICPCG members. LOD scores obtained from parametric analysis with use of a dominant model (*blue line*), a recessive model (*red line*), and nonparametric analysis (*yellow line*) are plotted by individual chromosome for the whole genome.

model was similar to the one used to map *HPC1* (MIM 601518) (Smith et al. 1996). The frequency of the susceptibility allele was assumed to be 0.003, with a penetrance of 0.001 for noncarriers and 1.0 for carriers. Unaffected subjects were coded as having noninformative phenotypes. The recessive model was similar to the dominant model, except that the susceptibility-allele frequency was set to 0.15 and the penetrance for heterozygous carriers was set equal to the penetrance for homozygous noncarriers. Stratified linkage analyses were also performed in two predetermined subsets of families: 269 families with at least five affected members, and 606 families with family mean age at diagnosis of ≤65 years. The planned analyses were developed and approved by members of the ICPCG.

We summarized our linkage results on the basis of the proposed guidelines for reporting linkage results of a genomewide screen: a cutoff LOD score of 3.30 as "significant" evidence of linkage and a cutoff LOD score of 1.86 as "suggestive" evidence of linkage (Lander and Kruglyak 1995). On the basis of asymptotic arguments, a LOD score of 3.30 is expected to occur 0.05 times in a genome screen that makes use of a fully informative marker set, and a LOD score of 1.86 is expected to occur once by chance.

Results

Analyses of All Families

Table 1 summarizes the characteristics of the 1,233 PC-affected families from 10 different ICPCG groups that were included in the analysis. Fifty-one percent of families had a mean age at onset of <65 years; 22% had five or more affected family members.

We first performed a combined genomewide linkage analysis of the complete set of 1,233 PC-affected families, using parametric and nonparametric approaches. Although no significant evidence of linkage was observed in the genome, evidence of suggestive PC linkage wasobserved at five chromosomal regions, 5q12, 8p21, 15q11, 17q21, and 22q12 (fig. 1 and table 2). The highest overall LOD score in the genome was 2.28 from the nonparametric analysis, found near marker *D5S2858* on

Table 2

Chromosomal Regions with Suggestive Evidence of Linkage

Population and Region	Distance from pter cM	Nearest Marker	Analysis Type	LOD	1-LOD Drop Interval Genetic (cM)	1-LOD Drop Interval Physical (Mb)
Primary analysis: entire set of families (N = 1,233):						
5q12	77	*D5S2858*	Nonparametric	2.28	66–96	43–78
8p21	46	*D8S1048*	Dominant	1.97	39–52	22–32
15q11	1	*D15S817*	Recessive	2.10	0–14	0–25
17q21	77	*D17S1820*	Dominant	1.99	66–85	35–54
22q12	42	*D22S283*	Dominant	1.95	35–47	29–37
Secondary analysis: subset of families with at least five affected family members (n = 269):						
1q25	184	*D1S2818*	Nonparametric	2.62	170–198	165–196
8q13	81	*D8S543*	Recessive	2.41	75–90	66–75
13q14	56	*D13S1807*	Recessive	2.27	42–67	39–71
16p13	34	*D16S764*	Nonparametric	1.88	19–46	9–23
17q21	77	*D17S1820*	Dominant	2.04	66–83	39–53
22q12	42	*D22S283*	Dominant	3.57	32–50	27–42
Secondary analysis: subset of families with mean age at diagnosis of ≤65 years (n = 606):						
3p24	57	*D3S2432*	Dominant	2.37	47–69	28–49
5q35	179	*D5S1456*	Dominant	2.05	166–193	162–174
11q22	102	*D11S898*	Recessive	2.20	89–112	81–111
Xq12	80	*DXS7132*	Dominant	2.30	62–90	40–85

5q12 (77 cM from pter). The linkage results for each individual family collection for each of these five chromosomal regions are shown in table 3. As seen in table 3, with the exception of 17q21, the LOD scores for each of the highlighted regions are higher in the combined analysis than those observed in any individual group, reaching a suggestive level of evidence only in the combined family data.

Analyses of Subsets of Families

We also performed linkage analyses in subsets of families that might be more likely to segregate genes conferring strong PC risk: families with at least five affected members or with family mean age at diagnosis of ≤65 years. As hypothesized, we found stronger evidence of linkage among 269 families with at least five affected members—one region with significant evidence of linkage and four additional regions with suggestive evidence of linkage (fig. 2 and table 2). The strongest evidence of linkage in the genome was found at 22q12 with use of the dominant model, with LOD score of 3.57 at 42 cM (near marker *D22S283*). This LOD score exceeded the criterion of significant evidence of linkage in the genomewide screen. Evidence of linkage at this region was provided by multiple ICPCG groups (fig. 3). Of the 10 groups, 4 had a LOD score >1.0 at this region, including a LOD score of 2.05 from the Mayo group, a LOD score of 1.57 from the Michigan group, a LOD score of 1.31 from the Utah group, and a LOD score of 1.22 from the JHU group. It is noted that linkage evidence at this region was observed in the complete set of 1,233 families (LOD score of 1.95 at 42 cM) and was strengthened

Table 3

Support for Linkage from Each Group at Chromosomal Regions with Suggestive Linkage

Population	LOD Score by Chromosomal Region and Model: 5q12 (77 cM) Nonparametric	8p21 (46 cM) Dominant	15q11 (1 cM) Recessive	17q21 (77 cM) Dominant	22q12 (42 cM) Dominant
All groups (N = 1,233)	2.28	1.97	2.10	1.99	1.95
ACTANE (n = 64)	.00	.00	.00	.00	.00
BC/CA/HI (n = 98)	1.17	.00	.26	.76	.00
JHU (n = 188)	.29	.16	.95	.72	1.28
Mayo Clinic (n = 159)	.32	.09	.00	.00	1.10
PROGRESS (n = 254)	.25	1.64	.64	.01	.00
University of Michigan (n = 176)	.01	.28	1.06	3.07	.13
University of Tampere (n = 10)	.00	.19	.00	.42	.02
University of Ulm (n = 139)	.38	.77	.04	.00	.00
University of Umeå (n = 50)	1.62	.00	.87	.00	.00
University of Utah (n = 95)	.27	.17	.00	.03	1.47

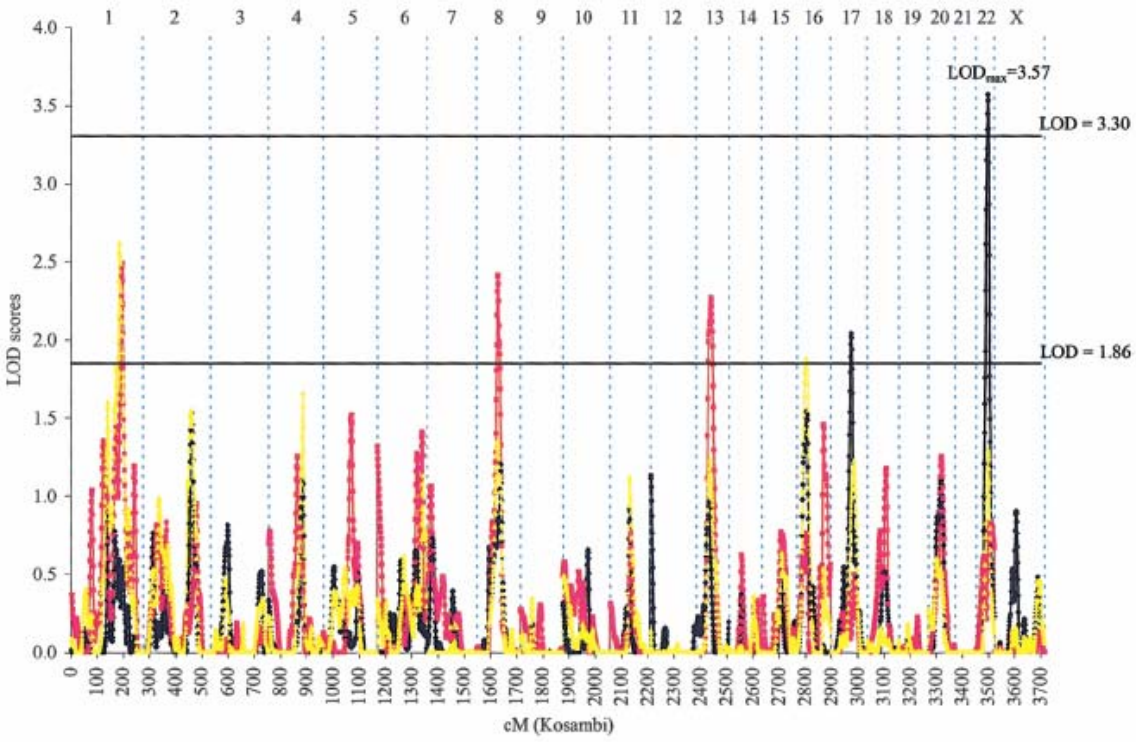

Figure 2 Combined genomewide screen for PC-susceptibility genes with use of nonparametric and parametric multipoint linkage analyses among 269 families with at least five affected members recruited from 10 ICPCG members. LOD scores obtained from parametric analysis with use of a dominant model (*blue line*), a recessive model (*red line*), and nonparametric analysis (*yellow line*) are plotted by individual chromosome for the whole genome.

in this subset. When families with at least five affected family members were removed from the analysis, no evidence of linkage at this region was found in the remaining 964 families. In addition to the 22q12 region, five additional regions reached suggestive evidence of PC linkage in this subset of families with at least five affected family members (fig. 2 and table 2).

For 606 families with family mean age at diagnosis of ≤65 years, suggestive evidence of PC linkage was found at four chromosomal regions (fig. 4 and table 2), with the highest LOD score of 2.37 near marker *D3S2432* at 3p24 (57 cM). The four PC linkages identified in this subset of families were unique to the early-age-at-diagnosis subset. No evidence of linkage at these four regions was observed in the complete set of 1,233 families.

Discussion

We have described results from the largest PC genomewide screen reported to date, with combined linkage data from 1,233 PC-affected families collected by 10 different groups in the ICPCG. From the primary analysis of the entire set of the families, we identified five chromosomal regions (5q12, 8p21, 15q11, 17q21, and 22q12) with suggestive evidence of linkage. With one exception (i.e., 17q21), the threshold for suggestive evidence of linkage was reached only in the combined analysis, which emphasizes the advantage of this combined approach.

Importantly, we found significant evidence of linkage at the 22q12 region in 269 families with at least five affected members, a subset of PC-affected families that is more likely to segregate mutations in genes conferring a strong PC risk. Suggestive evidence of linkage at five other regions (1q25, 8q13, 13q14, 16p13, and 17q21) was also observed in this subset of families. In addition, four additional regions (3p24, 5q35, 11q22, and Xq12) were found to have suggestive evidence of PC linkage in 606 families with family mean age at diagnosis of ≤65 years.

We recognize that many of the regions identified in this study may represent false positive findings due to multiple tests in a genomewide screen and that it is difficult to dissect true linkages from false signals. On the basis of the assumption of a fully informative marker

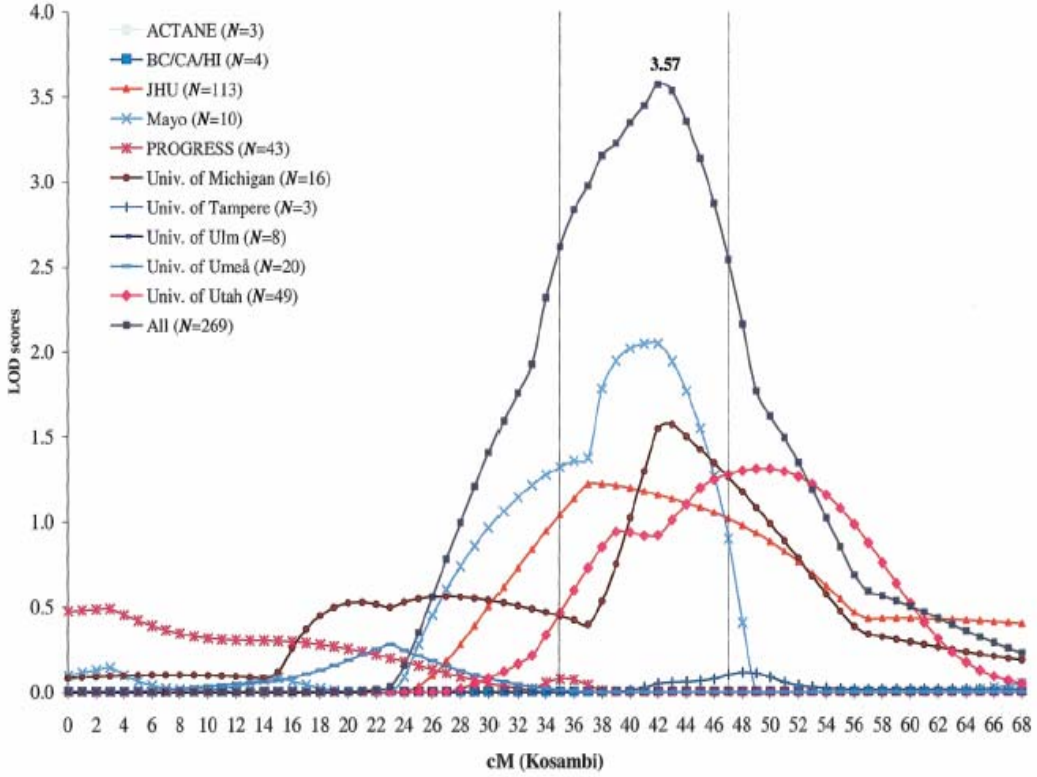

Figure 3 Parametric linkage analysis of chromosome 22 among families with at least five affected members with use of the dominant model. LOD scores are plotted for each of the 10 ICPCG groups.

map, LOD scores >3.30 or 1.86 would have been expected to occur 0.05 times and 1 time, respectively, in a single genomewide screen. Here, we performed nine genomewide screens (three in the primary analyses and six in the subgroup analyses); this needs to be considered when interpreting the results. However, these nine analyses are not independent. Using the method of Camp and Farnham (2001), we determined that the nine non-independent analyses performed were equivalent to ~5.2 independent genomewide screens. We therefore estimate that, after correcting for multiple testing, regions with a LOD score of >3.30 (significant evidence) in at least one analysis would be expected 0.25 times in 5.2 independent screens and regions with a LOD score of >1.86 (suggestive evidence), 5.2 times. Our empirical results (one observed LOD score of 3.57 and 13 regions with LOD scores ≥1.86) therefore exceeded the expectation under the null hypothesis of no linkage. Furthermore, these thresholds may be unduly conservative for the less-than-informative real data used in these genomewide screens. Although it is difficult to determine the true statistical significance of these findings, a conservative interpretation of these results would be that if major PC-susceptibility genes do exist, they are most likely to be located in the regions generating suggestive or significant linkage signals. Therefore, results from this analysis are likely to be helpful in prioritizing any efforts to identify PC-susceptibility genes.

Lack of reproducibility among PC-linkage studies in recent years demonstrates the difficulties faced in the effort to identify PC-susceptibility genes with the linkage approach (Isaacs and Xu 2002; Edwards and Eeles 2004; Ostrander et al. 2004; Schaid 2004). One of the major difficulties is genetic heterogeneity due to multiple but incompletely penetrant PC-susceptibility genes. Each of these genes may be responsible for a small fraction of PC-affected families. In this study, we planned two approaches to address the impact that these difficulties have on identification of PC linkage. One approach was to perform linkage analysis in a large number of PC-affected families, to increase the statistical power to detect linkage. This approach led to the identification of five regions with evidence suggestive of linkage in the complete set of 1,233 families. However, the failure to

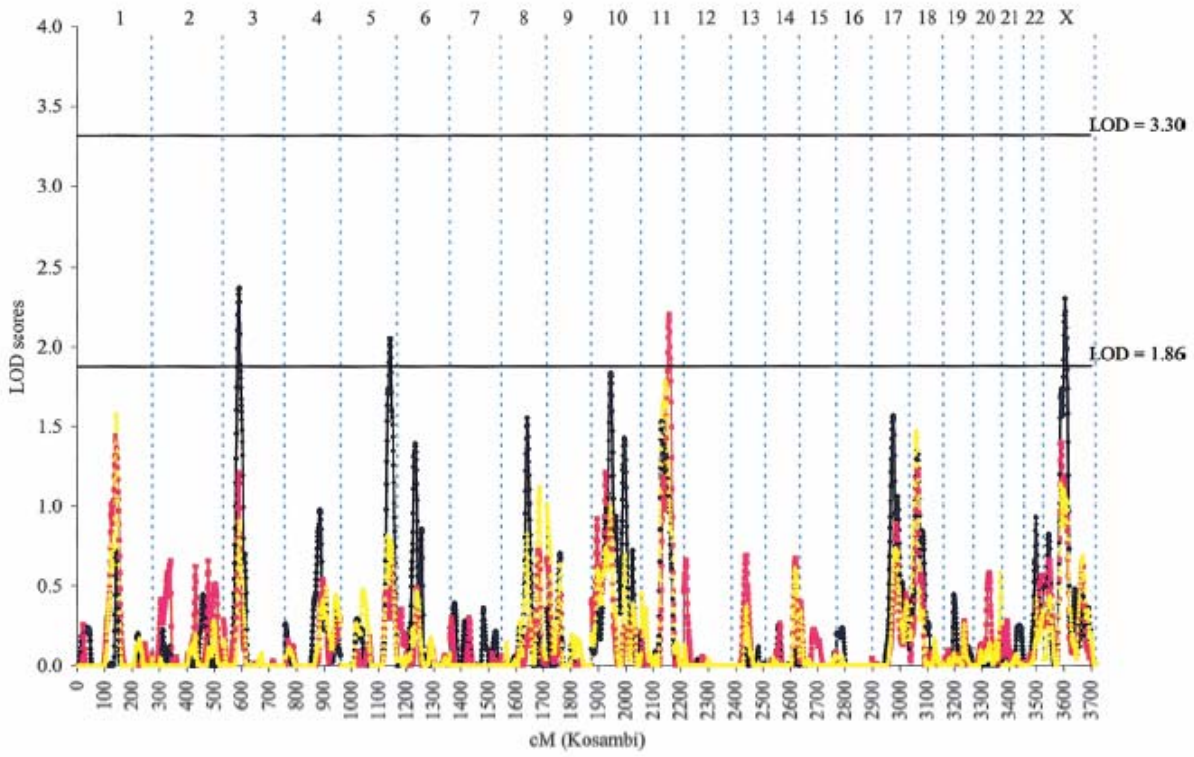

Figure 4 Combined genomewide screen for PC-susceptibility genes with use of nonparametric and parametric multipoint linkage analyses among 606 families with family mean age at diagnosis ≤65 years recruited from 10 ICPCG members. LOD scores obtained from parametric analysis with use of a dominant model (*blue line*), a recessive model (*red line*), and nonparametric analysis (*yellow line*) are plotted by individual chromosome for the whole genome.

identify significant linkage in the genome, even with this large number of families, indicates a substantial degree of genetic heterogeneity and suggests that this approach alone is insufficient to uncover a significant signal if it is present. Our second approach was to focus on subsets of families that are more likely to segregate highly penetrant mutations, including families with large numbers of affected individuals and/or early age at diagnosis. This latter approach appeared to be more effective; stronger evidence of linkage was found in several regions among these subsets of families than from the complete set of families. The most noteworthy finding was the considerable increase in evidence of linkage at 22q12—from a LOD score of 1.95 (suggestive linkage) in the complete set of families to a LOD score of 3.57 (significant linkage) in 269 families with at least five affected members. It is important to note that the large number of families in our combined study makes it possible to analyze sufficient numbers in each subset of families. Linkage studies in families with large numbers of affected individuals and/or early ages at diagnosis have proved to be effective in identifying breast cancer–susceptibility genes (Hall et al. 1990; Easton et al. 1993).

Three pieces of evidence from our study increase our confidence that the linkage at 22q12 is due to PC-susceptibility gene(s) at this region. First, the LOD score at this region reached the criterion of significant linkage. The chance of observing this magnitude of LOD score in the genome under a null hypothesis of no linkage is <0.25 times in our study. Second, this linkage was identified in the families with at least five affected members, a subset of families that is more likely to segregate mutations in genes conferring strong PC risk. Third, the evidence of linkage at this region was supported by multiple individual groups; of six groups with ≥10 such large families, four had LOD scores >1 in this interval. The relatively good reproducibility of this linkage finding is an unusual observation in PC-linkage studies (Easton et al. 2003). More than 129 known genes are in the 1-LOD drop interval (29–37 Mb). An important candidate gene, *CHEK2* (MIM 604373), is outside the interval, at ~27 Mb.

Because the mode of inheritance for PC is uncertain, we performed linkage analysis using both parametric (dominant or recessive) and nonparametric methods. In general, evidence of PC linkage was consistently provided by both parametric and nonparametric methods, although with different strengths at different regions. Parametric analysis will have better power to detect linkage when an assumed genetic model approximates the underlying mode of inheritance of a disease susceptibility gene (Clerget-Darpoux et al. 1986*a*, 1986*b*; Lio and Morton 1997). Nonparametric analysis, by assessment of allele sharing among affected individuals within a pedigree, may have better power when the underlying genetic model cannot be specified with any confidence (Whittemore and Halpern 1994).

Most of the linkage regions identified in the present study are broad. The information content of the marker sets used in these analyses is generally low, particularly since most of our families are small and often do not include genotypes of all parents. Further genotyping at a higher density, with use of either microsatellite markers or SNPs, should improve informativeness. An additional approach currently under way by the ICPCG incorporates clinical and pathological tumor variables in the assignment of affected status, to emphasize clinically aggressive disease in this large data set. Hopefully, these approaches should help to confirm or refute the evidence of linkage and narrow the regions of interest.

During the last decade, tremendous effort has been put forth to identify major susceptibility genes for PC. Linkage studies with smaller numbers of PC-affected families have identified and implicated many chromosomal regions that might harbor PC-susceptibility genes. The large number of different regions that have been implicated—and the general lack of reproducibility among these studies—has provided a tenuous foundation for subsequent PC-gene identification. In this context, results from the current study, with a very large number of families in the overall analysis, provides a strong basis for prioritizing regions for PC-gene identification.

Acknowledgments

We express our gratitude to the many families who participated in this study and to the many urologists who kindly assisted us by providing information and access to their patients. The ICPCG is supported by U.S. Public Health Service (USPHS) National Institutes of Health (NIH) grant CA89600. Additional support to participating groups or members within groups is as follows. ACTANE Group: Genotyping and statistical analysis for this study and recruitment of U.K. families was supported by Cancer Research U.K. Additional support was provided by the Prostate Cancer Charitable Trust (now Prostate Cancer Research Foundation), The Times Christmas Appeal, and the Institute of Cancer Research. Genotyping was conducted in the Jean Rook Gene Cloning Laboratory, which is supported by BREAKTHROUGH Breast Cancer–Charity 328323. The funds for the ABI 377 used in this study were generously provided by the legacy of the late Marion Silcock. We thank Mrs. Sheila Seal and Mrs. Anita Hall for kindly storing and logging the samples that were provided. D.F.E. is a principal research fellow of Cancer Research U.K. Recruitment of Australian PC-affected families was funded by National Health and Medical Research Council grant 940934 and was further supported by Tattersall's and the Whitten Foundation; infrastructure was provided by the Cancer Council Victoria. We acknowledge the work of study coordinator Margaret Staples; the research team of Bernadette McCudden, John Connal, Richard Thorowgood, Chris Costa, Melodie Kevan, and Sue Palmer; and Jolanta Karpowicz, for DNA extractions. The Texas study of familial PC was initiated by the Department of Epidemiology, M. D. Anderson Cancer Center. M.B. was supported by NCI post-doctoral fellowship in Cancer Prevention R25. BC/CA/HI Group: USPHS grant CA67044. JHU Group: USPHS grants CA58236 (to W.B.I.), CA95052-01 (to J.X.), and CA106523-01A1 (to J.X.). Mayo Clinic Group: USPHS grant CA72818. Michigan Group: USPHS grant CA079596. PROGRESS Group: USPHS grants CA78835 (to E.A.O.) and CA080122 (to J.L.S.) and support from the Prostate Cancer Foundation and the Fred Hutchinson Cancer Research Center (University of Washington Markey Center). Tampere Group: Medical Research Fund of Tampere University Hospital, Reino Lahtikari Foundation, Finnish Cancer Organizations, Sigrid Juselius Foundation, and Academy of Finland grant 201480. Ulm Group: Deutsche Krebshilfe grant 70–3111-V03. Umeå Group: Grants from the Swedish Cancer Society (Cancerfonden) and Stiftelsen för Strategisk Forskning. Utah Group: NIH NCI grant R01 CA90752 (to L.C.A.), a subcontract from JHU with funds provided by NIH NCI grant R01 CA89600 (to L.C.A.), and NIH grant K07 CA98364 (to N.C.). Data collection for this publication was assisted by the Utah Cancer Registry, supported by NIH Contract NO1-PC-35141 and Surveillance, Epidemiology and End Results Program, with additional support from the Utah Department of Health, the University of Utah, and Public Health Services research grant M01-RR00064 from the National Center for Research Resources. Partial support for all data sets within the Utah Population Database was provided by the University of Utah Huntsman Cancer Institute. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through federal NIH contract N01-HG-65403 (to J.H.U.). Genotyping for the JHU, Michigan, Tampere, and Umeå groups was performed by Elizabeth Gillanders, MaryPat Jones, Derk Gildea, Erica Riedesel, Julie Albertus, Diana Freas-Lutz, Carol Markey, John Carpten, and Jeff Trent at the National Human Genome Research Institute, NIH. Other investigators who contributed to this work: ACTANE: *United Kingdom (Sutton)*: Rifat Hamoudi, Audrey Ardern-Jones, Christine Southgate, Anna Dowe, Kim Coleman, David Dearnaley, The Cancer Research U.K./British Prostate Group U.K. Familial Prostate Cancer Study Collaborators, British Association of Urological Surgeons' Section of Oncology, Translational Cancer Genetics Team, Molecular Genetics Team, Section of Cancer Genetics; Institute of Cancer Research, Royal Marsden NHS

Trust Foundation Hospital. *United Kingdom (Cambridge)*: M. Dawn Teare, Cancer Research U.K. Genetic Epidemiology Unit, Strangeways Research Labs. *Australia*: Dallas English, Gianluca Severi, Melissa Southey, Cancer Epidemiology Centre, The Cancer Council Victoria; University of Melbourne, Centre for Genetic Epidemiology. *Canada*: Nancy Hamel, Division of Medical Genetics, Research Institute of the McGill University Health Centre, Montreal; Steven Narod, Centre for Research in Women's Health, University of Toronto, Toronto. *Texas*: Chris Amos, M. D. Anderson Cancer Centre, Houston. *Norway (Oslo)*: Ketil Heimdal Unit of Medical Genetics, Norwegian Radium Hospital, Oslo. *Norway (Ullevaal)*: Nicolai Wessel, Tone Andersen, Department of Oncology, Ullevaal University Hospital, Oslo. *EU Biomed*: The EU Biomed Prostate Cancer Linkage Consortium, Cancer Research U.K. Genetic Epidemiology Laboratory, St. James' University Hospital, Leeds. *JHU*: Piroska Bujnovszky, Tanya Ray, Vivian Bailey, Mary Buedel, and Dawn Steinberg. *Utah*: Alan Thomas, Lewis Ershler, and Kim Nguyen.

Author affiliations.—Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, NC (J.X., L.D., B.-L.C., T.S.A., A.R.T., and D.A.M.); Institute of Cancer Research and Royal Marsden National Health Service Trust Foundation Hospital, Sutton, United Kingdom (R.A.E., S.E., J.M., S.B., and Q.H.); Cancer Research U.K. Genetic Epidemiology Unit, Strangeways Research Labs, Cambridge, United Kingdom (D.F.E. and C.E.); Program in Cancer Genetics, Departments of Oncology and Human Genetics, McGill University, Montreal (W.D.F.); Cancer Genomics Laboratory, Centre hospitalier de l'Universite Laval Research Centre, Sainte-Foy, Quebec (J. Simard); University of Washington Medical Center (M.B. and G.P.J.) and Department of Medical Genetics, School of Public Health and Community Medicine, University of Washington (M.B. and G.P.J.), Divisions of Human Biology (D.M.F. and E.A.O.) and Public Health Sciences, Fred Hutchinson Cancer Center (S.K. and J.L.S.), and Institute for System Biology (K.D., M.J., and L.H.), Seattle; Cancer Epidemiology Centre, Cancer Council Victoria (G.G.G.), and Centre for Genetic Epidemiology, University of Melbourne (J.L.H.), Carlton, Australia; Unit of Medical Genetics, Norwegian Radium Hospital, Oslo (L.M. and P.M.); Cancer Research U.K. Genetic Epidemiology Laboratory, St. James' University Hospital, Leeds (T.B.); University of Southern California, Los Angeles (C.-I.H.); Stanford University School of Medicine, Stanford (J.H., R.N.B., and A.S.W.); Northern California Cancer Center, Union City and Stanford (I.O.-G.); Department of Urology, Johns Hopkins Medical Institutions (C.M.E., M.G., S.D.I. P.C.W., K.E.W., and W.B.I), and Inherited Disease Research Branch, National Human Genome Research Institute, NIH (J.B.-W.), Baltimore; Mayo Clinic, Rochester, MN (S.N.T., S.K.M., J.M.C., K.E.Z., S.H., and D.J.S.); Cancer Genetics Branch, National Human Genome Research Institute, (E.A.O.), and National Cancer Institute (NCI) (D.S.), NIH, Bethesda; Department of Genetics, University of North Carolina, Chapel Hill (E.M.L.); University of Michigan, Ann Arbor (J.L.B.-D., C.E.M., and K.A.C.); University of Tampere and Tampere University Hospital, Tampere, Finland (T.I., H.F., M.P.M. T.L.T., and J. Schleutker); Fox Chase Cancer Center, Division of Population Science, Philadelphia (A.B.-B.); Abteilung Humangenetik, Universität Ulm (C.M., J.J.H., and W.V.), and Urologische Universitätsklinik und Poliklinik, Abteilung für Urologie und Kinderurologie (K.H. and T.P.), Ulm, Germany; Department of Radiation Sciences, Oncology, University of Umeå, Umeå, Sweden (F.W., M.E., E.S., B.-A.J., and H.G.); Division of Genetic Epidemiology, University of Utah, Salt Lake City (N.J.C., J.F., and L.C.A).

Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PC, *ELAC2, RNASEL, MSR1, HPC1,* and *CHEK2*)

References

Camp NJ, Farnham JM (2001) Correcting for multiple analyses in genomewide linkage studies. Ann Hum Genet 65:577–582

Camp NJ, Farnham JM, Cannon-Albright LA. Genome search for prostate cancer predisposition loci in Utah pedigrees. Prostate (in press)

Carpten J, Nupponen N, Isaacs S, Sood R, Robbins C, Xu J, Faruque M, et al (2002) Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat Genet 30:181–184

Clerget-Darpoux F, Bonaiti-Pellie C, Hochez J (1986*a*) Effects of misspecifying genetic parameters in lod score analysis. Biometrics 42:393–399

Clerget-Darpoux F, Dizier MH, Bonaiti-Pellie C, Babron MC, Hochez J, Martinez M (1986*b*) Discrimination between genetic models for insulin dependent diabetes mellitus. Genet Epidemiol Suppl 1:313–318

Cunningham JM, McDonnell SK, Marks A, Hebbring S, Anderson SA, Peterson BJ, Slager S, French A, Blute ML, Schaid DJ, Thibodeau SN (2003) Genome linkage screen for prostate cancer susceptibility loci: results from the Mayo Clinic Familial Prostate Cancer Study. Prostate 57:335–346

Easton DF, Bishop DT, Ford D, Crockford GP (1993) Breast Cancer Linkage Consortium: genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. Am J Hum Genet 52:678–701

Easton DF, Schaid DJ, Whittemore AS, Isaacs WJ (2003) Where are the prostate cancer genes? A summary of eight genome wide searches. Prostate 57:261–269

Edwards SM, Eeles RA (2004) Unravelling the genetics of prostate cancer. Am J Med Genet C Semin Med Genet 129:65–73

Hall JM, Lee MK, Newman B, Morrow JE, Anderson LA, Huey B, King MC (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. Science 250:1684–1689

Hsieh C-l, Oakley-Girvan I, Balise RR, Halpern J, Gallagher RP, Wu AH, Kolonel LN, O'Brien LE, Lin IG, Van Den Berg DJ, Teh C-Z, West DW, Whittemore AS (2001) A genome screen of families with multiple cases of prostate cancer: evidence of genetic heterogeneity. Am J Hum Genet 69:148–158

Isaacs WB, Xu J (2002) Prostate cancer. In: King RA, Totter JI, Motulsky AG (eds) The genetic basis of common diseases. Oxford University Press, New York

International ACTANE Consortium (2003) Results of a genome-wide linkage analysis in prostate cancer families ascertained through the ACTANE consortium. Prostate 57:270–279

Janer M, Friedrichsen DM, Stanford JL, Badzioch MD, Kolb S, Deutsch K, Peters MA, Goode EL, Welti R, DeFrance HB, Iwasaki L, Li S, Hood L, Ostrander EA, Jarvik GP (2003) Genomic scan of 254 hereditary prostate cancer families. Prostate 57:309–319

Kong A, Cox NJ (1997) Allele-sharing models: LOD scores and accurate linkage tests. Am J Hum Genet 61:1179–1188

Kong A, Gudbjartsson D, Sainz J, Jonsdottir G, Gudjonsson S, Richardsson B, Sigurdardottir S, Barnard B, Hallbeck B, Masson M, Shlien A, Palsson S, Frigge M, Thorgeirsson T, Gulcher J, Stefansson K (2002) A high-resolution recombination map of the human genome. Nat Genet 31:241–247

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lander E, Kruglyak L (1995) Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 11:241–247

Lange EM, Gillanders EM, Davis CC, Brown WM, Campbell JK, Jones M, Gildea D, Riedesel E, Albertus J, Freas-Lutz D, Markey C, Giri V, Dimmer JB, Montie JE, Trent JM, Cooney KA (2003) Genome-wide scan for prostate cancer susceptibility genes using families from the University of Michigan prostate cancer genetics project finds evidence for linkage on chromosome 17 near BRCA1. Prostate 57:326–334

Lio P, Morton NE (1997) Comparison of parametric and nonparametric methods to map oligogenes by linkage. Proc Natl Acad Sci USA 94:5344–5348

Maier C, Herkommer K, Hoegel J, Vogel W, Paiss T (2005) A genomewide linkage analysis for prostate cancer susceptibility genes in families from Germany. Eur J Hum Genet 13:352–360

Ostrander EA, Markianos K, Stanford JL (2004) Finding prostate cancer susceptibility genes. Annu Rev Genomics Hum Genet 5:151–175

Ott J (1999) Analysis of human genetic linkage. The Johns Hopkins University Press, Baltimore

Schaid D (2004) The complex genetic epidemiology of prostate cancer. Hum Mol Genet 13:R103–R121

Schaid DJ, Chang BL, International Consortium for Prostate Cancer Genetics (2005) Description of the international consortium for prostate cancer genetics, and failure to replicate linkage of hereditary prostate cancer to 20q13. Prostate 63: 276–290

Schleutker J, Baffoe-Bonnie AB, Gillanders E, Kainu T, Jones MP, Freas-Lutz D, Markey C, Gildea D, Riedesel E, Albertus J, Gibbs KD Jr, Matikainen M, Koivisto PA, Tammela T, Bailey-Wilson JE, Trent JM, Kallioniemi OP (2003) Genome-wide scan for linkage in Finnish hereditary prostate cancer (HPC) families identifies novel susceptibility loci at 11q14 and 3p25-26. Prostate 57:280–289

Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, Isaacs SD, Brownstein MJ, Bova GS, Guo H, Bujinovszky P, Nusskern DR, Damber JE, Bergh A, Emanuelsson M, Kallioniemi OP, Walker-Daniels J, Bailey-Wilson JE, Beaty TH, Meyers DA, Walsh PC, Collins FS, Trent JM, Isaacs WB (1996) Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science 274:1371–1374

Tavtigian S, Simard J, Teng D, Abtin V, Baumgard M, Beck A, Camp N, et al (2001) A strong candidate prostate cancer susceptibility gene at chromosome 17p. Nat Genet 27:172–180

Whittemore AS, Halpern J (1994) A class of tests for linkage using affected pedigree members. Biometrics 50:118–127

Wiklund F, Gillanders EM, Albertus JA, Bergh A, Damber JE, Emanuelsson M, Freas-Lutz DL, Gildea DE, Goransson I, Jones MS, Jonsson BA, Lindmark F, Markey CJ, Riedesel EL, Stenman E, Trent JM, Grönberg H (2003) Genome-wide scan of Swedish families with hereditary prostate cancer: suggestive evidence of linkage at 5q11.2 and 19p13.3. Prostate 57:290–297

Xu J, Gillanders EM, Isaacs SD, Chang BL, Wiley KE, Zheng SL, Jones M, Gildea D, Riedesel E, Albertus J, Freas-Lutz D, Markey C, Meyers DA, Walsh PC, Trent JM, Isaacs WB (2003) Genome-wide scan for prostate cancer susceptibility genes in the Johns Hopkins hereditary prostate cancer families. Prostate 57:320–325

Xu J, Zheng SL, Komiya A, Mychaleckyj JC, Isaacs SD, Hu JJ, Sterling D, et al (2002) Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Nat Genet 32:321–325

Hum Genet (2006) 120:471–485
DOI 10.1007/s00439-006-0219-9

ORIGINAL INVESTIGATION

Pooled genome linkage scan of aggressive prostate cancer: results from the International Consortium for Prostate Cancer Genetics

Daniel J. Schaid · Investigators of the International Consortium for Prostate Cancer Genetics

Received: 8 March 2006 / Accepted: 5 June 2006 / Published online: 25 August 2006

Abstract While it is widely appreciated that prostate cancers vary substantially in their propensity to progress to a life-threatening stage, the molecular events responsible for this progression have not been identified. Understanding these molecular mechanisms could provide important prognostic information relevant to more effective clinical management of this heterogeneous cancer. Hence, through genetic linkage analyses, we examined the hypothesis that the tendency to develop *aggressive* prostate cancer may have an important genetic component. Starting with 1,233 familial prostate cancer families with genome scan data available from the International Consortium for Prostate Cancer Genetics, we selected those that had at least three members with the phenotype of clinically aggressive prostate cancer, as defined by either high tumor grade and/or stage, resulting in 166 pedigrees (13%). Genome-wide linkage data were then pooled to perform a combined linkage analysis for these families. Linkage signals reaching a suggestive level of significance were found on chromosomes 6p22.3 (LOD = 3.0), 11q14.1–14.3 (LOD = 2.4), and 20p11.21–q11.21 (LOD = 2.5). For chromosome 11, stronger evidence of linkage (LOD = 3.3) was observed among pedigrees with an average at diagnosis of 65 years or younger. Other chromosomes that showed evidence for heterogeneity in linkage across strata were chromosome 7, with the strongest linkage signal among pedigrees without male-to-male disease transmission (7q21.11, LOD = 4.1), and chromosome 21, with the strongest linkage signal among pedigrees that had African American ancestry (21q22.13–22.3; LOD = 3.2). Our findings suggest several regions that may contain genes which, when mutated, predispose men to develop a more aggressive prostate cancer phenotype. This provides a basis for attempts to identify these genes, with potential clinical utility for men with aggressive prostate cancer and their relatives.

The names of all authors and their affiliations are listed in the Acknowledgements. The fact that Dr Schaid's name is given here for purposes of correspondence should not be taken to imply that he played the sole leading part in writing this article.

D. J. Schaid (✉)
Harwick 7, Mayo Clinic College of Medicine,
200 First ST SW, Rochester, MN 55905, USA
e-mail: schaid@mayo.edu

Introduction

There is much evidence that prostate cancer, the most frequent of all cancers in men (Jemal et al. 2004), has a familial, if not genetic, etiology. This evidence is supported by a variety of study designs, including case–control, cohort, twin, and family-based studies (Grönberg 2003; Schaid 2004), although linkage studies to find genes associated with high prostate cancer risk have been disappointing. Early linkage results implicated targeted candidate regions for prostate cancer susceptibility loci, including HPC1 on chromosome 1q23–25 (Smith et al. 1996; Xu 2000; Carpten et al. 2002), PCAP on chromosome 1q42–43 (Berthon et al. 1998), CAPB on chromosome 1p36 (Gibbs et al. 1999), chromosome 8p22–23 (Xu et al. 2001), HPC2 on chromosome 17p (Tavtigian et al. 2001), HPC20 on chromosome 20q13 (Berry et al. 2000), and HPCX on chromosome Xq27–28 (Xu et al. 1998). A few of the targeted linkage studies have led to the identification

of candidate susceptibility genes including RNASEL (HPC1) on chromosome 1 (Carpten et al. 2002), ELAC2 (HPC2) on chromosome 17 (Tavtigian et al. 2001), and MSR1 on chromosome 8 (Xu et al. 2002). Despite these promising findings, however, confirmatory studies for these genes have provided mixed results. A number of studies provide strong support, both functional and epidemiological, while other studies suggest that the roles of these genes, in terms of individual risks and/or prevalence of mutations, might be small (Ostrander and Stanford 2000; Schaid 2004).

In addition to targeted linkage analyses, at least 12 genome linkage scans based on microsatellite markers have now been performed (Easton et al. 2003; Matsui et al. 2004; Schaid 2004; Camp et al. 2005). Overall, the cumulative data across all of these studies show some suggestive evidence for linkage to almost every chromosome. Although there is some overlap among studies for chromosomal regions that show suggestive to moderate evidence for linkage, there is no evidence for a single (or a common few) major susceptibility loci. In total, these studies illustrate the difficulty in finding consistent linkage results across different studies and emphasize the likely large amount of genetic heterogeneity of prostate cancer risk. Furthermore, these results suggest that if linkage analysis is to be used successfully to identify prostate cancer susceptibility genes, innovative approaches to address such extensive genetic heterogeneity will be required.

The diagnosis of prostate cancer is common—in the U.S. approximately one in six men is diagnosed with prostate cancer in his lifetime. The *development* of prostate cancer is even more common—estimates from autopsy studies indicate that between 40 and 70% of men over age 70 will have cancer in their prostates, at least in the form of histologically identifiable lesions. It is clear that only a subset of these lesions are detected clinically and that only a subset of these clinically detected cancers will progress to life-threatening disease. A recent study of the use of prostate-specific antigen (PSA) to screen for prostate cancer estimated that 15–37% of men are overdiagnosed with prostate cancer, meaning that they have clinically insignificant prostate cancer that otherwise would not be detected in their lifetime (Etzioni et al. 2002). Correspondingly, identification of genetic factors that affect the aggressiveness of prostate cancers is an important question both mechanistically and clinically. Most previous attempts to identify prostate cancer susceptibility genes using linkage analysis have focused on families with multiple members affected with prostate cancers regardless of clinical-pathologic characteristics. The few studies that focused on families with men diagnosed with clearly aggressive disease have been hampered by the small number of families available within individual study samples. To overcome these limitations, we used genome-wide linkage to evaluate evidence for linkage in a set of unique families, each with at least three men affected with aggressive prostate cancer.

From a genetic perspective, it is unclear whether so-called clinically insignificant cancers share the same molecular risk factors as their aggressive counterparts. If they do, it is important to understand the molecular determinants of risk for all prostate cancers, although such factors would likely be extremely common, since the disease is so common, at least in most western populations. On the other hand, if genetic susceptibility for more aggressive prostate cancer is mediated through different, or additional, mechanisms, it is important to characterize those specific mechanisms and identify the genes involved. From a clinical perspective, it is important to understand the predisposition to an aggressive form of the disease, because such cancers can cause disability and death if not effectively treated.

Supporting our hypothesis that the more aggressive prostate cancers are more likely to have a genetic cause, several studies have found linkage of Gleason grade to a number of genomic regions. Gleason grade is used to measure prostate tumor differentiation and is considered a measure of cancer aggressiveness. Although the Gleason sum scale ranges from 2 to 10, most tumors are scored in a much more narrow range, most commonly 6 and 7. Using Gleason grade in quantitative trait linkage analyses, the reported linkage regions include chromosomes 5q31–33, 7q32, and 19q12 (Witte et al. 2000; Neville et al. 2002, 2003; Paiss et al. 2003), 9q34 (Neville et al. 2003), 4 (Slager et al. 2003), and 1p13–q21, 5p13–q11, and 6q23 (Slager et al. 2006). Furthermore, two recent studies reported interesting linkage signals from genome linkage scans restricted to men with clinically aggressive prostate cancer. One recent study (Chang et al. 2005) reported suggestive evidence for linkage on chromosome X (HLOD = 2.54) and on chromosome 22 (HLOD = 2.06), while another (Stanford et al. 2006) found suggestive evidence for linkage on chromosome 22 (dominant HLOD = 2.18). Although neither study found a LOD score greater than 3.0, the criterion typically used to define statistically significant linkage, it is intriguing that both studies were consistent for their findings on chromosome 22. Since the above-mentioned studies were carried out on limited numbers of families, the power to detect linkage in restricted subsets of families with aggressive disease was limited.

Because it has not been possible to discover prostate cancer susceptibility genes, and considering our

hypothesis that aggressive prostate cancer may be more genetically homogeneous, we used the International Consortium for Prostate Cancer Genetics (ICPCG) to pool pedigrees that had at least three men with aggressive prostate cancer. Pooling was necessary to obtain a sufficiently large sample size to perform a genome-wide linkage scan. Other pooled analyses by the ICPCG have been used to evaluate linkage for prostate cancer not restricted to the aggressive phenotype on chromosomes 1 (Xu 2000) and 20 (Schaid and Chang 2005), as well as a pooled genome linkage scan (Xu et al. 2005).

Methods

Ascertainment of pedigrees

The ICPCG study sample has been described in detail elsewhere (Schaid and Chang 2005; Xu et al. 2005). Eleven research groups participated in this combined linkage analysis of aggressive prostate cancer pedigrees, providing 166 pedigrees. Although the methods of pedigree ascertainment and confirmation of prostate cancer diagnoses differed somewhat across the groups, only men with aggressive prostate cancer diagnosis confirmed by medical records or death certificates were included in this analysis.

Definition of aggressive disease

Clinical data were used to classify affected men into three groups according to the aggressiveness of their prostate cancer. The classification criteria, presented in Table 1, were developed by the ICPCG Epidemiology subcommittee and are similar to those used in other recent linkage analyses of clinically significant disease (Chang et al. 2005; Stanford et al. 2006). Men with aggressive prostate cancer were those who had at least one of the following characteristics: regional or distant stage (stage T3, T4, N1, or M1, based on the radical prostatectomy specimen for patients treated with surgery; otherwise, based on clinical stage); tumor Gleason grade at diagnosis ≥ 7 (or poorly differentiated grade if no Gleason grade was available); pretreatment PSA at diagnosis ≥ 20 ng/ml; death from metastatic prostate cancer before age 65 years (if deceased).

Pedigrees were included in the analyses if they had three or more men with aggressive disease, of whom at least two men had aggressive disease and genotype data. Men with aggressive disease were coded as affected, and all other subjects were coded as unknown phenotype (i.e., men with clinically insignificant and moderate disease did not contribute their phenotypes to the linkage analyses). This approach avoids the complication of unaffected men who have not been screened for prostate cancer, and avoids attempting to model the unknown parameters that might influence the penetrance of less aggressive prostate cancers. Hence, we focused solely on evidence for genetic linkage to aggressive disease.

Each participating group submitted to the Data Coordinating Center (DCC) summary information about each pedigree, including mean age at diagnosis of aggressive disease, number of men with aggressive disease who had genotype data, hereditary prostate cancer (HPC), and male-to-male transmission of prostate cancer. A pedigree was classified as HPC if it met the criteria of Carter et al. (1993). At least one of the following three criteria must have been met: (1) three consecutive generations of prostate cancer along a line of descent; (2) at least three first-degree relatives with a diagnosis of prostate cancer; (3) two or more relatives with a diagnosis of prostate cancer at age ≤55

Table 1 Definition of prostate cancer aggressiveness

Insignificant: a subject was classified as having had clinically insignificant disease if he had *all* of the following characteristics:
- Clinically unapparent tumor at diagnosis (stage A, NOS, T1a, T1b, or T1c)
- Tumor in only one lobe if radical prostatectomy was done (T2a)
- No evidence of non-localized disease (node negative NX or N0; no metastasis, M0, confined to prostate, T2a)
- Tumor Gleason grade at diagnosis < 6; if no Gleason grade, then not moderately or poorly differentiated
- Pretreatment PSA at diagnosis < 4 ng/ml
- If deceased, prostate cancer not listed as primary cause of death on death certificate

Aggressive: a subject was classified as having had aggressive disease if he had *any* of the following characteristics:
- Regional or distant stage (stage T3, T4, N1, or M1, based on pathology if radical prostatectomy was done; otherwise, clinical stage)
- Tumor Gleason grade at diagnosis ≥ 7
- Poorly differentiated grade (if no Gleason grade available)
- Pretreatment PSA at diagnosis ≥ 20 ng/ml
- If deceased, death from metastatic prostate cancer before age 65 years

Moderate: a subject was classified as having had moderate disease if clinical data were available and he did not meet the criteria for insignificant or aggressive disease

years. Furthermore, because linkage of prostate cancer susceptibility to chromosome X has been reported (Xu et al. 1998), pedigrees were classified according to male-to-male transmission (yes versus no). Pedigrees classified as "yes" were consistent with autosomal dominant transmission, allowing for incomplete penetrance. For example, pedigrees were classified as "yes" if a father and son both had prostate cancer, or if the father was unaffected, but paternal cousins both had prostate cancer. All other pedigrees were classified as "no"; this means that the "no" group includes pedigrees that have a clear pattern of X-linked transmission and pedigrees that did not have sufficient information to distinguish incomplete penetrance for an autosomal dominant susceptibility allele versus X-linked transmission (e.g., nuclear families with unaffected fathers).

Genotyping and consensus genetic map

The participating groups used a total of 1,322 microsatellite markers, although the genotype methods and the sets of markers differed across the groups. Details of the genotype methods and construction of a consensus map are given elsewhere (Xu et al. 2005). Briefly, a consensus map was created by aligning all markers to the draft human reference sequence (physical position) based on the Human hg13 assembly (released November 14, 2002). Ten of these markers could not be uniquely located in the human reference sequence and were dropped from the combined analysis. The genetic positions of the aligned markers were determined from the deCode map (Kong et al. 2002). Among the 1,312 mapped markers, the deCode genetic position was available for 964 markers. The genetic positions for the remaining 348 markers, where only physical positions were available, were estimated by interpolation between the flanking markers where both physical positions and deCode positions were available.

Statistical analyses

Linkage analyses were performed by each of the 11 groups using common methods of analysis. Output files from Genehunter-Plus (Kruglyak et al. 1996; Kong and Cox 1997) containing pedigree-specific linkage information at 1 cM intervals across the genome were sent to the ICPCG DCC. The analyses were developed and approved by members of the ICPCG and are described in detail elsewhere (Schaid and Chang 2005). Both parametric and non-parametric linkage analyses were performed. For parametric analyses, dominant and recessive models were used. The dominant model, the same as that used to map HPC1 (Smith et al. 1996), had two liability classes. Men with aggressive prostate cancer were placed in the first liability class with penetrances of 0.001 and 1.0 for non-carriers and carriers, respectively. All other subjects were placed in a second uninformative liability class, i.e., assigned penetrance of 0.5 for all genotypes. Hence, analyses were for aggressive affecteds only, yet other family members with genotypes helped to infer the missing genotypes among parents. The frequency of the susceptibility allele was set at 0.003. The recessive model was similar to the dominant model, except that the susceptibility allele frequency was set at 0.15, and the penetrances for heterozygous carriers and homozygous non-carriers were assumed to be equivalent. These model-based analyses allowed for a fraction of linked pedigrees by computing heterogeneity LOD scores using the algorithm of HOMOG, estimating a single fraction of linked pedigrees (α) for all positions on a chromosome (HLOD-DOM for the dominant model and HLOD-REC for the recessive model). For the non-parametric analyses, Kong and Cox LOD scores for the linear (KCLOD-LIN) and exponential (KCLOD-EXP) allele-sharing models were calculated by the ASM software (Kong and Cox 1997). Pedigrees were weighted equally, and the score function "all" was used. All linkage results were based on multipoint calculations by the Genehunter-Plus software (Kruglyak et al. 1996; Kong and Cox 1997).

Because some studies suggest that early age at prostate cancer diagnosis increases the likelihood of a genetic etiology, and some families fit an autosomal dominant mode of transmission (see reviews by Grönberg 2003; Schaid 2004) we attempted to create genetically homogeneous subsets. To do this, we stratified pedigrees according to mean age at diagnosis of aggressive prostate cancer (≤ 65, > 65 years), number of men with both aggressive prostate cancer and genotype data per pedigree (< 4 versus 4+), evidence of HPC for any type of prostate cancer, as defined elsewhere (Carter et al. 1993), and racial ancestry. Furthermore, pedigrees were classified according to male-to-male transmission of any form of prostate cancer ("yes" versus "no").

Like others, we computed the maximum LOD scores within subsets. However, using this strategy alone can be misleading. The magnitude of the maximum LOD score depends on the number of pedigrees and their information content. Strata with more informative pedigrees, and a larger number of them, can give larger linkage signals than other less-informative strata. Thus, it would be incorrect to interpret the results to indicate that only the strata with

large linkage signals show evidence for linkage. Furthermore, examining multiple subsets can inflate the false-positive rate. To avoid these problems, there should be significant heterogeneity of the linkage signals across strata, because one would not expect to find heterogeneity in the absence of linkage. Hence, to aid our interpretations, we tested for statistically significant different linkage signals across strata by likelihood ratio statistics, constructed as follows. For the parametric HLOD statistics, we allowed each stratum to have its own parameter representing the fraction of linked pedigrees within the stratum (α_k), yet we assumed that all strata share the same position of linkage on a chromosome (θ). For K strata there were $(K+1)$ parameters to estimate. Under the null hypothesis of homogeneity across strata, there were only two parameters to estimate, the common value of α and θ. By maximizing the HLOD functions under the null hypothesis ($HLOD_{null}$) and under the alternative hypothesis ($HLOD_{alt}$), we computed a likelihood ratio statistic, $2(HLOD_{alt} - HLOD_{null})$, and used the χ^2_{K-1} distribution to determine probability values. Similar likelihood ratio statistics were computed using the KC LOD scores.

To illustrate the amount of heterogeneity of linkage, we present the estimated α parameters for each stratum. Statistically significant heterogeneity can arise from differences in the α parameters. However, the estimated α's must be viewed cautiously, because they are most likely biased. Bias can occur when the assumed penetrance is not correct (e.g., when penetrance varies over etiologically relevant genes), when the phenocopy rate is misspecified, and the likelihood used in HOMOG is not correct for estimating α (Whittemore and Halpern 2001).

We summarized our linkage results based on the proposed guidelines for reporting linkage results of a genome-wide screen: a cutoff of LOD = 3.30 as "significant" evidence for linkage, and a cutoff of LOD = 1.86 as "suggestive" evidence for linkage (Lander and Kruglyak 1995). Based on asymptotic arguments, a LOD score of 3.30 is expected to occur 0.05 times in a genome screen using a fully informative marker set and a LOD score of 1.86 is expected to occur once by chance.

Although computing *P*-values for extreme linkage statistics by simulations is an ideal way to evaluate the statistical significance of large LOD scores, we could not compute these by the usual methods that rely on the raw genotype and phenotype data. The data were collected during a period of time when informed consents did not request sending data to a central location, and some institutions felt that they would need to reconsent participants in order to submit their raw data to a central location. To overcome this limitation, we computed empirical *P*-values in a limited (i.e., conservative) manner. To compute permutation *P*-values, we use the rapid permutation strategy for score statistics proposed by Lin (2005). He showed that under the null hypothesis, and conditional on the data, permutation *P*-values can be computed by multiplying an observed score statistic for an observation (in our case, each pedigree is an observation) by a standard normal random variable, and then computing the desired summary statistic. In our application, the NPL scores per pedigree are score statistics for the Kong and Cox allele-sharing models (both linear and exponential) (Kong and Cox 1997). So, for each of 10,000 simulations, we generated a random normal variable per pedigree, multiplied the observed NPL scores by the random variable, computed the summary NPL over all pedigrees, and then determined the maximum summary statistic over all positions on a chromosome. The method by Lin is appropriate when the different statistics (e.g., maximum LOD scores per chromosome) have the same null distribution. However, this is not the case, because longer chromosomes are more likely to have larger LOD scores than shorter chromosomes, because longer chromosomes have less dependence due to more recombinations. This can be verified by asymptotic approximations given elsewhere (Feingold et al. 1993). Hence, we computed permutation *P*-values separately for each chromosome, and then used Benjamini and Hochberg's (Benjamini and Hochberg 1995) step-up method to determine *P*-values corrected for testing multiple chromosomes while controlling the false-discovery rate. An advantage of this approach is that by conditioning on the observed NPL scores, it implicitly conditions on the linkage information in a pedigree, in contrast to other approaches that assume fully informative markers for simulations. A limitation, however, is that it is well known that NPL summary statistics have less power than the Kong and Cox LOD scores when linkage information is not complete. Hence, our reported permutation *P*-values are likely too large, compared to what might be achieved with the raw data.

Results

The characteristics of the 166 aggressive prostate cancer pedigrees from the 11 groups of the ICPCG are summarized in Table 2. Among these pedigrees, 44% had a mean age at diagnosis of 65 years or younger, 27% had at least four men with aggressive prostate

Table 2 Characteristics of the ICPCG pedigrees used for aggressive prostate cancer linkage

ICPCG member	Mean age at aggressive disease diagnosis (years)		No. with aggressive disease and genotype data		Hereditary prostate cancer		Male-to-male		Race			Total no. of pedigrees
	≤ 65	> 65	2–3	4+	No	Yes	Yes	No	African American	Other	Caucasian	
ACTANE		1	1			1		1			1	1
BC/CA/HI	1	2	3		1	2	1	2	2		1	3
JHU	10	13	16	7		23	20	3	2		21	23
Mayo Clinic	8	10	15	3	10	8	10	8			18	18
Fred Hutchinson/ISB	17	20	27	10	7	30	17	20	1	2	34	37
University of Michigan	14	8	17	5	8	14	14	8	3	1	18	22
Washington University	4	4	6	2	1	7	7	1		1	7	8
University of Tampere	2	2		4		4	3	1			4	4
University of Ulm	9	5	13	1	3	11	7	7			14	14
University of Umeå	1	7	7	1	1	7	2	6			8	8
University of Utah	7	21	16	12	17	11	25	3			28	28
All	73	93	121	45	48	118	107	59	8	4	154	166

cancer and genotype data, 71% met the Carter criteria for HPC, and 92% had Caucasian ancestry (8 pedigrees had African American ancestry; 1 pedigree, Asian; 1 pedigree, Hispanic; 2 pedigrees, Native American).

The linkage results for the pool of all 166 pedigrees are summarized in Table 3. Suggestive linkage results (LOD scores > 1.86) were observed on chromosomes 6p, 11q, and 20p. See Fig. 1 for plots of LOD scores for these chromosomes. The largest LOD scores were found at chromosome 6p22.3, with KCLOD-LIN = 3.00 and KCLOD-EXP = 2.63 (42 cM). The recessive model HLOD-REC was 2.20 in this region of chromosome 6 (43 cM). At chromosome 11q14.1–14.3, the recessive model HLOD-REC was 2.40 (89 cM), with weaker evidence provided by the allele-sharing models (KCLOD-LIN = 1.81 and KCLOD-EXP = 1.91 at 88 cM). At chromosome 20p11.21–q11.21, the largest LOD score was an HLOD-DOM of 2.49 (54 cM). The permutation *P*-values are consistent with these findings, with chromosome 6 having the smallest *P*-value ($P = 0.004$; pFDR = 0.08), and chromosomes 11 ($P = 0.017$; pFDR = 0.196) and 20 ($P = 0.057$; pFDR = 0.263) less significant. However, because chromosome 20 showed the largest LOD score by the dominant model, the true level of statistical significance for chromosome 20 is not well approximated by the permutation *P*-values, which are based on the NPL scores.

Heterogeneity across strata and subset results

Our results from evaluating heterogeneity across strata suggested that there might be heterogeneity for six chromosomes: chromosomes 5, 6, 7, 11, 20, and 21. As summarized in Table 4, the linkage results for these chromosomes varied substantially according to the strata analyzed. See also Fig. 1 for the LOD scores plotted within each of the strata for these chromosomes. Three of these six chromosomes were those for which suggestive linkage evidence was found in the pool of all 166 pedigrees: chromosomes 6, 11, and 20. For chromosomes 6 and 20, the stronger linkage signals were found in the subset of pedigrees with an average age at diagnosis greater than 65 years; for chromosome 6, the strongest linkage signal was KCLOD-LIN = 2.74, while for chromosome 20, the strongest linkage signal was HLOD-DOM = 2.65. In contrast, for chromosome 11, the strongest linkage signal was for pedigrees with an average age at diagnosis of 65 years or younger, with HLOD-REC = 3.31.

The three other chromosomes that showed evidence for heterogeneity across strata were chromosomes 5, 7, and 21. Chromosomes 5 and 7 showed the strongest linkage signal among pedigrees without male-to-male disease transmission (5q21.2–22.1, KCLOD-LIN = 2.24; 7q21.11, HLOD-DOM = 4.09). Chromosome 21q22.13–22.3 showed the strongest linkage signal for pedigrees that had African American ancestry (HLOD-DOM = 3.19). Each of these subset linkage signals was located within approximately 5 cM of the maximum LOD score observed in the full set of pedigrees for the corresponding chromosomes (Table 3).

Previous linkage to chromosome 20 has been reported by the Mayo Clinic group (Berry et al. 2000), of which 18 of the original Mayo Clinic pedigrees were

Table 3 Maximum LOD scores for each chromosome

Chromosome	Allele-sharing exponential model		Allele-sharing linear model		Simulation *P*-values		Dominant model			Recessive model		
	KCLOD-EXP	cM	KCLOD–LIN	cM	Empiric	FDR	HLOD	cM	α	HLOD	cM	α
1	0.53	156	0.60	154	0.556	0.765	0.34	158	0.07	0.43	188	0.09
2	0.82	83	0.82	83	0.398	0.765	0.99	67	0.10	0.99	66	0.13
3	0.24	171	0.26	168	0.760	0.832	0.05	34	0.02	0.55	175	0.11
4	1.42	0	1.43	0	0.192	0.568	1.25	0	0.24	1.09	0	0.26
5	1.39	96	1.64	101	0.041	0.233	0.87	85	0.14	1.19	117	0.16
6[a]	2.63	42	3.00	42	0.004	0.080	1.21	43	0.15	2.20	43	0.25
7	0.47	32	0.45	33	0.484	0.765	0.43	32	0.07	1.02	35	0.14
8	0.89	136	0.78	136	0.242	0.618	1.17	137	0.15	0.79	136	0.15
9	0.21	46	0.26	46	0.714	0.832	0.12	137	0.05	0.57	110	0.10
10	0.34	81	0.23	95	0.667	0.832	0.97	81	0.08	0.75	81	0.10
11[a]	1.91	88	1.81	88	0.017	0.196	0.71	78	0.11	2.40	89	0.23
12	1.81	21	1.82	21	0.033	0.233	1.61	21	0.19	0.83	22	0.15
13	0.33	123	0.26	123	0.545	0.765	1.00	123	0.13	0.83	123	0.13
14	0.02	91	0.02	91	0.930	0.930	0	0	0	0.08	94	0.03
15	0.25	80	0.30	122	0.566	0.765	0.14	133	0.06	0.50	81	0.11
16	0.49	39	0.48	39	0.341	0.765	0.92	25	0.13	0.77	40	0.14
17	0.32	48	0.27	48	0.539	0.765	0.38	50	0.07	0.48	47	0.10
18	0.74	97	0.84	98	0.196	0.568	0.35	91	0.07	0.51	95	0.11
19	0.11	36	0.10	36	0.732	0.832	0.29	37	0.06	0.10	77	0.05
20[a]	1.43	52	1.16	52	0.057	0.263	2.49	54	0.18	1.48	52	0.16
21	0.01	79	0.01	79	0.844	0.882	0	0	0	0.14	78	0.09
22	0.20	23	0.14	23	0.490	0.765	0.79	19	0.11	0.61	18	0.13
X	0.94	134	0.93	133	0.198	0.568	1.00	139	0.15	0.94	136	0.24

[a] Chromosomes with LOD scores > 2.0

also included in this analysis. Excluding these 18 Mayo Clinic pedigrees resulted in an HLOD-DOM of 1.85 on chromosome 20, suggesting that the pedigrees with aggressive prostate cancer from the remaining ICPCG members contribute a large fraction to this linkage signal. Furthermore, two of the groups participating in this pooled analysis recently reported their own genome-wide linkage scans for aggressive prostate cancer [Johns Hopkins University (Chang et al. 2005); Fred Hutchinson Cancer Center/Institute of Systems Biology (Stanford et al. 2006)]. To determine whether our findings were influenced by the pedigrees from these prior studies, and to determine the influence from each group, we analyzed the linkage signals for each group that had at least ten pedigrees; all groups with fewer pedigrees were combined into a single "others" group. The heterogeneity results presented in Table 5 illustrate significant heterogeneity across groups for chromosomes 1 and 2, but not for the regions on chromosomes 6, 11, and 20. For chromosome 1, the heterogeneity was most obvious for the dominant model, with pedigrees from Johns Hopkins, Mayo Clinic, and University of Michigan giving the largest LOD scores. For chromosome 2, the recessive model gave the largest heterogeneity, with pedigrees from the "others" group giving the largest LOD score, followed by pedigrees from the Mayo Clinic.

Discussion

Our main findings, based on the pool of 166 pedigrees with aggressive prostate cancer, were statistically significant evidence for linkage for chromosome 6 and suggestive linkage signals, with LOD scores at least 2.0, on chromosomes 11, and 20. In the stratified analyses, we found evidence for significantly different linkage signals across strata for these three chromosomes, and in some strata, the linkage signals for chromosomes 11 and 20 increased. In fact, the strongest signal was at chromosome 11q14.1–14.3, from the 73 pedigrees with younger ages at diagnosis. From a genetic perspective, this is enticing: the strength of familial risks for prostate cancer are greater for earlier age at diagnosis (Johns and Houlston 2003). The stratified analyses provided additional interesting linkage signals on chromosomes 5, 7, and 21.

A hallmark of genetically inherited cancer syndromes is the tendency for cancers to begin, or at least become clinically detectable, at an earlier age than

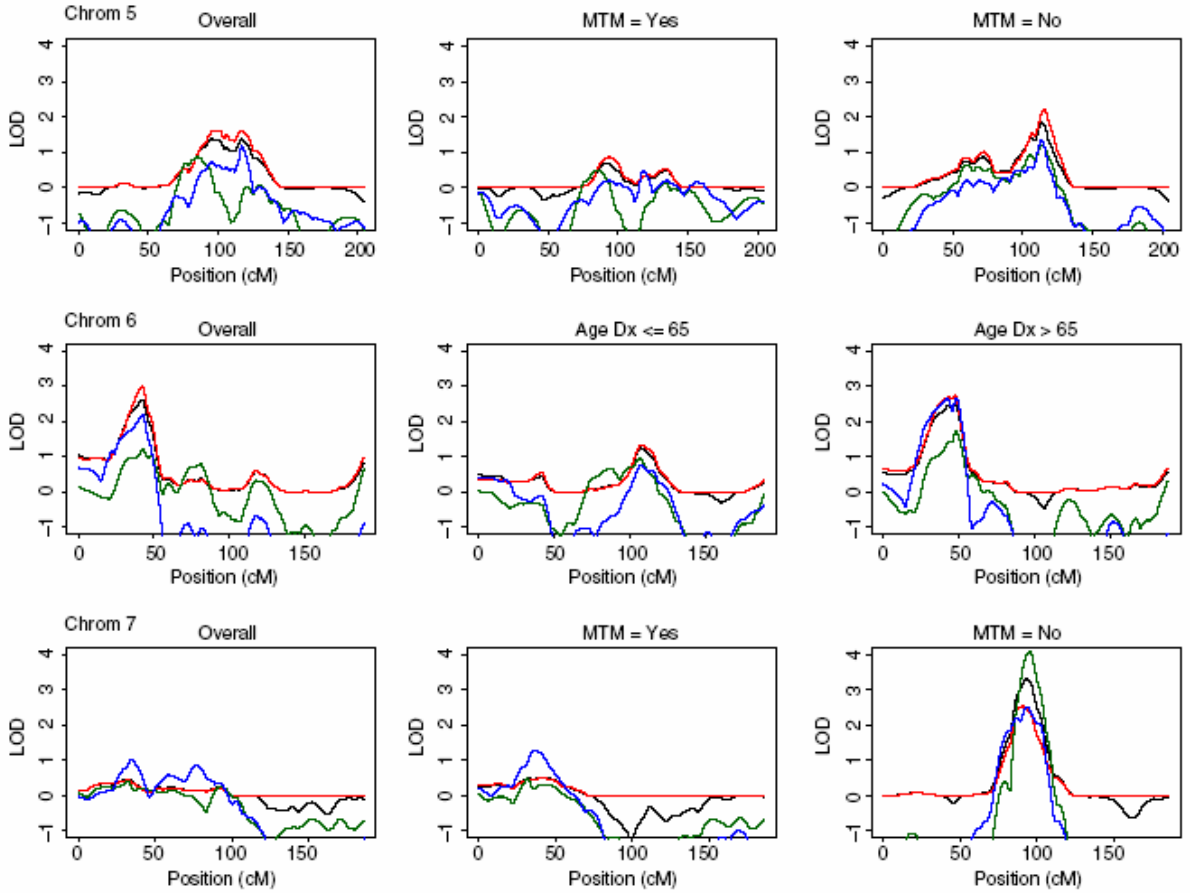

Fig. 1 LOD scores for chromosomes and strata with statistically significant linkage heterogeneity and LOD scores > 2 in at least one stratum—chromosomes 5, 6, 7, 11, 20, and 21 (*MTM* male-to-male transmission of prostate cancer, *Age Dx* age at diagnosis). The *line colors* represent different linkage tests (see figure legend)

their non-genetic counterparts (Lindor et al. 1998). For this reason, age at diagnosis is frequently used as a potential indicator of inherited prostate cancers. However, age at diagnosis is a poor surrogate for age at onset of prostate cancer, because age at diagnosis is strongly influenced by screening practices. For example, a man not previously screened for prostate cancer, yet diagnosed at age 70 with metastatic prostate cancer, possibly could have been diagnosed 10–20 years earlier had he been screened for prostate cancer. A man diagnosed at age 55 with a low-volume, low-grade cancer may be just one of the substantial proportion of men of this age in the general population who have within their prostates small amounts of cancerous cells that have minimal clinical significance. On the other hand, if this latter man had such extensive cancer that it was no longer confined to the prostate, it would suggest that the cancer had been present for a number of years, and it was "early-onset" disease. Therefore, our focus on clinically aggressive prostate cancer not only emphasizes a clinically important phenotype, but also, in the case of aggressive disease at an early age, it increases the likelihood that we are studying truly early-onset disease. Using families that have multiple men affected with aggressive disease provides an opportunity to enrich the study sample for genetic influences that may be detectable by linkage analysis. Our finding of a LOD score greater than 3.3 in families with aggressive disease at an early age is particularly interesting in this respect.

To assess the strength of evidence for our regions of interest, we reviewed 21 reports that published genome-wide linkage scans for prostate cancer. Two studies, like ours, restricted their analyses to only aggressive prostate cancers (Chang et al. 2005; Stanford et al. 2006). Four studies screened for linkage by using Gleason grade as a quantitative trait (Witte et al. 2000, 2003; Slager et al. 2003, 2006). Finally, the majority of

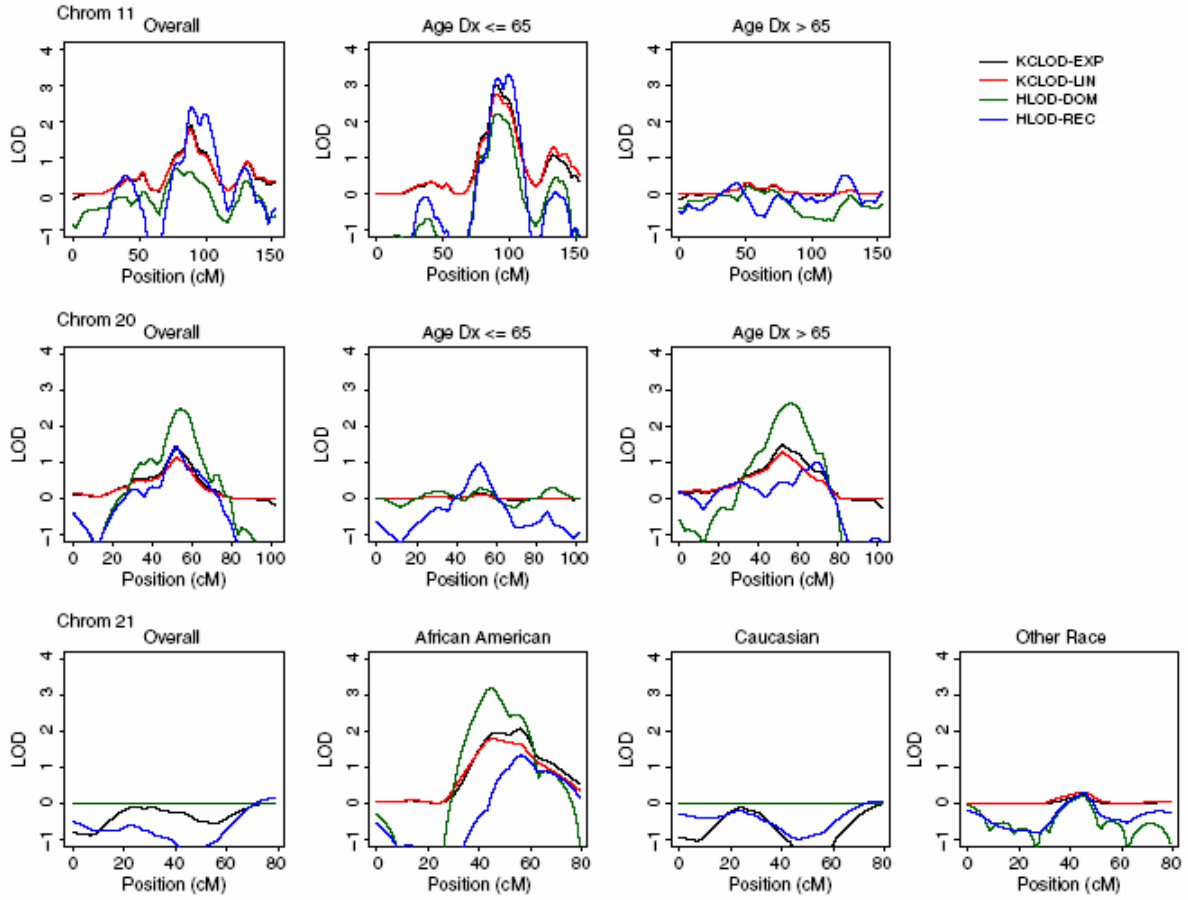

Fig. 1 continued

studies—15—analyzed any type of prostate cancer (Smith et al. 1996; Suarez et al. 2000; Goddard et al. 2001; Hsieh et al. 2001; Cunningham et al. 2003; Edwards et al. 2003; Janer et al. 2003; Lange et al. 2003; Schleutker et al. 2003; Wiklund et al. 2003; Xu et al. 2003; Gillanders et al. 2004; Matsui et al. 2004; Camp et al. 2005; Xu et al. 2005). These studies are not all independent, because some represent expanded accrual over prior studies, and some represent analyses combined over multiple groups. Many of these reports are from members of the ICPCG; the report by Xu et al. (2005) is a pooled analysis of any form of prostate cancer among 1,233 pedigrees from ten groups of the ICPCG. To quantify the linkage evidence as LOD scores, results reported as P-values were converted to LOD scores for this discussion. This conversion is $\mathrm{LOD} = \chi^2_{1,1-2P}\log_{10}(e)/2$ where $\chi^2_{1,1-2P}$ is the quantile of a chi-square distribution with one degree of freedom, at the percentile $1-2P$, P is the P-value, and e is the base of the natural logarithm. A summary of chromosomes that had LOD scores at least 2.0 for our chromosomes of interest is given in Table 6.

For chromosome 5, Stanford et al. (2006)—who restricted their analyses to the aggressive disease phenotype—found a suggestive linkage signal among pedigrees classified as not having HPC (following Carter's criteria). A number of studies have found similar evidence for linkage near this same region. Slager et al. (2006) reported a similar linkage signal using Gleason grade as a quantitative trait, Goddard et al. (2001) found similar linkage evidence using Gleason grade as a covariate, and Wiklund et al. (2003) found similar evidence among men from Sweden. It is worth emphasizing that in this Swedish study approximately two-thirds of the men were diagnosed with prostate cancer before 1990 when PSA was introduced as an aid to early detection, and 79% of the men had clinical symptoms at diagnosis. This suggests that the men in the Swedish

Table 4 Summary of chromosomes and strata with significant heterogeneity over strata and LOD scores >2 in at least one stratum

Chromosome	Strata	No. ped.	KC-EXP		KC-LIN		DOM			REC		
			LOD	cM	LOD	cM	HLOD	α	cM	HLOD	α	cM
5	MTM[a]											
	Yes	107	0.69	93	0.87	94	0.50	0.13	86	0.51	0.12	118
	No	59	1.85 (0.10)	114	2.24 (0.048)	116	1.20 (0.80)	0.29	114	1.34 (0.47)	0.30	113
6	Dx age											
	≤ 65	73	1.26	107	1.32	108	0.99	0.22	107	0.77	0.23	107
	> 65	93	2.47 (0.28)	48	2.74 (0.30)	48	1.72 (0.039)	0.23	48	2.68 (0.10)	0.36	49
7	MTM											
	Yes	107	0.52	42	0.50	42	0.49	0.08	32	1.29	0.20	37
	No	59	3.31 (0.002)	93	2.54 (0.002)	91	4.09 (0.02)	0.49	96	2.51 (0.61)	0.43	94
11	Dx age											
	≤ 65	73	3.02	90	2.76	90	2.22	0.32	90	3.31	0.44	100
	> 65	93	0.30 (0.022)	53	0.33 (0.035)	53	0.23 (0.10)	0.08	53	0.52 (0.91)	0.15	124
20	Dx age											
	≤ 65	73	0.18	52	0.14	52	0.32	0.08	89	0.99	0.17	52
	> 65	93	1.49 (0.29)	52	1.29 (0.27)	52	2.65 (0.045)	0.26	56	1.01 (0.27)	0.18	69
21	African American	8	2.08	56	1.79	45	3.19	1.0	45	1.35	1.0	56
	Caucasian	154	−0.03	79	0.00	79	0.00	0	79	0.06	0.06	79
	Other	4	0.25 (0.11)	45	0.31 (0.008)	45	0.21 (0.05)	1.0	45	0.30 (0.29)	0.73	45

Maximum LOD scores by chromosome and strata. *P*-values to test heterogeneity over strata are enclosed in parentheses

[a] Male-to-male transmission of prostate cancer

study have more aggressive disease than those in the typical linkage study performed elsewhere.

At approximately 80 cM distant from this region on chromosome 5, Witte et al. (2000) reported suggestive linkage at 5q31–33. It is interesting that in an independent follow-up study, Witte et al. (2003) reported a LOD score of 1.6 at 5p15, approximately 150 cM distant from their initial finding. This large variation in chromosome position of the largest linkage signal is clearly illustrated in Table 6 for most of the chromosomes of interest. Finally, when analyzing any form of prostate cancer, both Camp et al. (2005) and Xu et al. (2005) reported suggestive linkage signals on chromosome 5 among pedigrees with an earlier age at diagnosis.

For chromosome 6, Stanford et al. (2006), using the aggressive disease phenotype, found a suggestive linkage signal among pedigrees with an earlier age at diagnosis. Slager et al. (2006), using Gleason grade as a quantitative trait, found a similar linkage signal in this same region. The University of Michigan group recently completed a genome scan of their 71 pedigrees

Table 5 Summary of chromosomes and strata with significant heterogeneity over ICPCG Member Groups and LOD scores > 2 in at least one stratum

Chromosome	Strata	No. ped.	KC-EXP		KC-LIN		DOM			REC		
			LOD	cM	LOD	cM	HLOD	α	cM	HLOD	α	cM
1	Fred Hutchinson/ISB	37	0.14	159	0.17	159	0.05	0.05	195	0.52	0.21	188
	JHU	23	2.17	150	2.06	72	2.65	0.73	152	2.14	0.75	64
	University of Ulm	14	0.88	247	1.00	247	0.21	0.20	47	0.50	0.46	246
	Mayo Clinic	18	1.53	271	1.31	271	1.86	0.51	271	0.88	0.48	271
	University of Michigan	22	1.33	182	0.92	182	0.96	0.36	183	1.60	0.50	184
	University of Utah	28	0.79	66	0.75	66	0.64	0.24	59	0.30	0.28	28
	Others	24	0.51 (0.26)	187	0.18 (0.13)	188	0.37 (0.05)	0.22	188	0.34 (0.27)	0.23	186
2	Fred Hutchinson/ISB	37	0.39	19	0.33	19	0.87	0.24	25	0.48	0.18	210
	JHU	23	0.08	55	0.08	55	0.28	0.19	89	0.05	0.09	89
	University of Ulm	14	0.39	204	0.35	204	0.42	0.32	171	0.31	0.23	165
	Mayo Clinic	18	0.62	50	0.85	230	0.50	0.29	49	0.96	0.42	67
	University of Michigan	22	0.86	205	0.87	211	1.12	0.42	202	0.34	0.27	204
	University of Utah	28	0.54	96	0.59	94	0.58	0.14	67	0.43	0.34	102
	Others	24	1.70 (0.43)	77	2.13 (0.21)	77	1.47 (0.44)	0.56	77	2.41 (0.05)	0.69	78

Maximum LOD scores by chromosome and strata. *P*-values to test heterogeneity over strata are enclosed in parentheses

Table 6 Summary of published LOD scores at least 2.0 for chromosomes 5, 6, 7, 11, and 20

Chromosome	Type of PC	LOD	cM	Nearest marker	Stratum or covariate	Reference
5	Aggressive	2.0	69	D5S2500	HPC = no	Stanford et al. (2006)
	Gleason as QTL	2.1	65	D5S407		Slager et al. (2006)
	Gleason as QTL	2.4	147	D5S1480		Witte et al. (2000)
	Any	2.3	56	D5S1457	Gleason as covariate	Goddard et al. (2001)
	Any	2.2	65	D5S407	All pedigrees	Wiklund et al. (2003)
	Any	2.1	110	D5S1503	Dx age ≤ 69	Camp et al. (2005)
	Any	2.3	77	D5S2858	All pedigrees	Xu et al. (2005)
	Any	2.0	179	D5S1456	Dx age ≤ 65	Xu et al. (2005)
6	Aggressive	2.2	125	D6S1040	Dx age ≤ 58	Stanford et al. (2006)
	Gleason as QTL	2.1	137	D6S292		Slager et al. (2006)
	Any	3.9	185	D6S281	Dx age ≥ 66	Cunningham et al. (2003)
	Any	2.5	25	D6S1281	All pedigrees	Janer et al. (2003)
7	Aggressive	3.2	7	D7S3056	N. affected ≥ 5	Stanford et al. (2006)
	Aggressive	2.1	42	D7S1824	Dx age > 65	Paiss et al. (2003)
	Gleason as QTL	2.2	130	D7S1804		Witte et al. (2000)
	Gleason as QTL	2.1	130	D7S1804	Expansion of above study	Witte et al. (2003)
	Any	2.3	96	D7S2212	All pedigrees	Janer et al. (2003)
11	Any	3.4	88	D11S901	All pedigrees	Schleutker et al. (2003)
	Any	2.2	102	D11S898	All pedigrees	Xu et al. (2005)
	Any	2.1	123	D11S4464	All pedigrees	Witte et al. (2003)
20	Aggressive	2.6	27	ATTC013	MTM = no	Stanford et al. (2006)
	Any	4.8	78	D20S196	All pedigrees	Cunningham et al. (2003)

MTM male-to-male transmission of prostate cancer, *HPC* hereditary prostate cancer

with aggressive prostate cancer. Their inclusion criteria were more liberal than those used in this study, because Lange et al. (2006) included pedigrees with only two men with aggressive disease. They had 49 such pedigrees, while 22 of their pedigrees with at least three men with aggressive disease overlapped with this current pooled analysis. Their strongest signal, on chromosome 15q, was driven entirely by the 49 families with only two men with aggressive prostate cancer, while their second largest linkage signal, on chromosome 6p, was similar for those families included versus those not included in this current pooled analysis. Their 49 excluded pedigrees had a LOD score of approximately 1.2 in the chromosome 6p22–23 region (E.M. Lange, personal communication). When analyzing any form of prostate cancer, the ACTANE group (Edwards et al. 2003) found a LOD score over 1.0 on 6p for a large number of families that did not meet the more strict criteria of this pooled analysis. Furthermore, Janer et al. (2003) found a linkage signal approximately 100 cM distant from these other reports. Cunningham et al. (2003) found a strong linkage signal on 6p among men with an older age at diagnosis. These regions varied from our region at 6p22.3—at approximately 50 cM—that had a LOD score of 3.0. This region is approximately 20 cM distant to HLA, which resides at 6p21.3. Perhaps this ties with the speculation that immunity and inflammatory mechanisms play a critical role in the development of prostate cancer (Nelson et al. 2004).

For chromosome 7, Stanford et al. (2006), using the aggressive disease phenotype, found a suggestive linkage signal among pedigrees with at least five men with prostate cancer. The linkage signal, however, was approximately 90 cM distant from a prior report by this group that found suggestive linkage for chromosome 7 when analyzing any form of prostate cancer (Janer et al. 2003). In contrast, when restricted to men with an aggressive disease and an older age at diagnosis, Paiss et al. (2003) reported a suggestive linkage signal that was only about 35 cM from that reported by Stanford et al. When analyzing Gleason grade as a quantitative trait, Witte et al. found linkage signals at approximately 130 cM (Witte et al. 2000, 2003), much closer to the position of 96 cM reported by Janer et al. Further support for chromosome 7q32 comes from finding an increased allelic imbalance in primary prostate tumors (Neville et al. 2002).

For chromosome 11, both Schleutker et al. (2003) and Witte et al. (2003) reported interesting LOD scores at about the same locations, and an ICPCG pooled analysis confirmed these findings (Xu et al. 2005). Although Schleutker et al. (2003) did not restrict their pedigrees to only men with aggressive disease, they did skew their selected pedigrees to have as many affected men as possible (at least 3 per pedigree), and out of the 13 pedigrees used in their initial findings for chromosome 11, 4 met the present criteria for aggressive prostate cancer to be included in our current

analyses. Furthermore, like the Swedish families, many of the Finnish families were diagnosed prior to the use of PSA screening that started in early 1990s in Finland. Among the original families used for linkage, 32% of the patients were diagnosed before 1990, and 42% had clinical symptoms at diagnosis.

For chromosome 20, Stanford et al. (2006), using the aggressive disease phenotype, found a suggestive linkage signal among pedigrees without male-to-male transmission. The position of this linkage signal was about 30 cM distant from the large linkage signal that Cunningham et al. (2003) reported when analyzing any form of prostate cancer. Unfortunately, the findings by Cunningham et al. could not be replicated by a pooled ICPCG study; a LOD score of 0.06 was found among 1,076 pedigrees not included in the original Mayo Clinic study (Schaid and Chang 2005). These results suggest that focusing on aggressive prostate cancer may reveal linkage that is not apparent among all types of prostate cancers.

Our finding of a linkage signal for chromosome 21 among eight pedigrees with African American ancestry is intriguing, yet no other studies reported LOD scores greater than 2.0 for chromosome 21. This suggests that our finding may be spurious. A possible cause of a spurious finding is that the founders of our pedigrees, typically parent and grand-parent generations, do not have DNA available for genotyping. Hence, our statistical analyses depend on estimated allele frequencies. Because each group had few non-Caucasian pedigrees, each group estimated allele frequencies in the pool of all their pedigrees. If these allele frequencies differed between the majority of the Caucasian pedigrees and the African American pedigrees, then this could lead to bias, and possibly falsely inflated LOD scores in the African American pedigrees.

In contrast to our summary of linkage signals that have been reported for our regions of interest, it is worthwhile to consider reported linkage signals for the aggressive disease phenotype that we did not detect. Using a similarly defined aggressive disease phenotype, Chang et al. found a LOD score of 2.5 for chromosome X and a LOD score of 2.1 for chromosome 22 (Chang et al. 2005). They also found interesting, yet less striking, signals on chromosomes 3 and 9. Stanford et al. also found an interesting signal on chromosome 22, a LOD score of 2.2 (Stanford et al. 2006). The University of Michigan group, that also focused on aggressive prostate cancer, recently found a LOD score of 3.5 at chromosome 15q12 (Lange et al. 2006). Other regions reported to have suggestive linkage signals when analyzing Gleason grade as a quantitative trait are chromosomes 4 and 15 (Slager et al. 2003), chromosome 9 (Witte et al. 2003) and chromosome 19 (Witte et al. 2000; Neville et al. 2002, 2003).

In summary, our linkage findings for aggressive prostate cancer that seem to be most consistent with prior published studies are chromosomes 5q, 6p, 7q, and 11q. These results suggest that prostate cancer aggressiveness might be controlled by multiple genes. Although the major strength of our study is the large number of pedigrees with aggressive prostate cancer, we recognize that our selection criteria means our conclusions are likely to be relevant more for disease with an earlier age at disease onset; requiring metastatic disease or death from prostate cancer implies an earlier age at onset, because it takes time for metastases and death to occur. Nonetheless, we chose our study design because we believed it would enrich for HPC. Like many genetically complex traits, resolving the genetic basis of prostate cancer is likely to require large studies, much like ours based on the ICPCG, as well as novel experimental designs and analyses. Our findings provide directions for future studies to target candidate genes for aggressive prostate cancer, based on our strongest linkage findings for chromosomes 6 and 11, and possibly 20.

Acknowledgments We would like to express our gratitude to the many families who participated in this study and to the many urologists who kindly assisted us by providing information and access to their patients. All members of the ICPCG are supported by the U.S. Public Health Service (USPHS), National Institutes of Health (CA89600). Additional support to participating groups, or members within groups, follows. *ACTANE Group*: Genotyping and statistical analysis for this study and recruitment of U.K. families was supported by Cancer Research U.K. Additional support was provided by the Prostate Cancer Charitable Trust (now Prostate Cancer Research Foundation), The Times Christmas Appeal, and the Institute of Cancer Research. Genotyping was conducted in the Jean Rook Gene Cloning Laboratory, which is supported by BREAKTHROUGH Breast Cancer-Charity 328323. The funds for the ABI 377 used in this study were generously provided by the legacy of the late Marion Silcock. We thank Mrs Sheila Seal and Mrs Anita Hall for kindly storing and logging the samples that were provided. D.F.E. is a principal research fellow of Cancer Research U.K. Recruitment of Australian PC-affected families was funded by National Health and Medical Research Council grant 940934 and was further supported by Tattersall's and the Whitten Foundation; infrastructure was provided by the Cancer Council Victoria. We acknowledge the work of study coordinator Margaret Staples; the research team of Bernadette McCudden, John Connal, Richard Thorowgood, Chris Costa, Melodie Kevan, and Sue Palmer; and Jolanta Karpowicz, for DNA extractions. The Texas study of familial PC was initiated by the Department of Epidemiology, M.D. Anderson Cancer Center. M.B. was supported by NCI post-doctoral fellowship in Cancer Prevention R25. Additional support to W.D.F. was supplied by grant DAMD-17-00-10033. *BC/CA/HI Group*: USPHS CA67044. *JHU Group*: USPHS CA58236 (W.B.I.), CA95052-01 (J.X.), CA106523-01A1 (J.X.). Genotyping for the

JHU, Michigan, Tampere, and Umeå groups were performed by Elizabeth Gillanders, MaryPat Jones, Derk Gildea, Erica Riedesel, Julie Albertus, Diana Freas-Lutz, Carol Markey, John Carpten, and Jeff Trent at the National Human Genome Research Institute, NIH. *Mayo Clinic Group*: USPHS CA72818. *Michigan Group*: USPHS CA079596. *Fred Hutchinson/ISB Group*: USPHS CA78835 (E.A.O.), CA080122 (J.L.S.), and from the Prostate Cancer Foundation and the Fred Hutchinson Cancer Research Center. *Tampere Group*: Medical Research Fund of Tampere University Hospital, Reino Lahtikari Foundation, Finnish Cancer Organizations, Sigrid Juselius Foundation and Academy of Finland (grant number 201480). *Ulm Group*: Deutsche Krebshilfe, grant number 70-3111-V03. *Umeå Group*: Grants from the Swedish Cancer Society (Cancerfonden) and Stiftelsen för Strategisk Forskning. *Utah Group*: NIH National Cancer Institute grant number R01 CA90752 (to L.A.C.). National Institutes of Health grant number K07 CA98364 (to N.J.C.). Data collected for this publication was assisted by the Utah Cancer Registry supported by National Institutes of Health Contract NO1-PC-35141, Surveillance, Epidemiology and End Results (SEER) Program, with additional support from the Utah Department of Health and the University of Utah. Partial support for all datasets within the Utah Population Database (UPDB) was provided by the University of Utah Huntsman Cancer Institute. Public Health Services research grant number M01-RR00064 from the National Center for Research Resources. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number N01-HG-65403. *Washington University Group*: Urological Research Foundation.

Mayo Clinic
Authors: Daniel J. Schaid, Shannon K. McDonnell, Katherine E. Zarfas, Julie M. Cunningham, Scott Hebbring, Stephen N. Thibodeau
Affiliations: Mayo Clinic, Rochester, MN, USA (D.J.S., S.K.M, K.E.Z, J.M.C., S.H., and S.N.T.)

ACTANE
Authors: Rosalind A. Eeles, Douglas F. Easton, William D. Foulkes, Jacques Simard, Graham G. Giles, John L. Hopper, Lovise Mahle, Pal Moller, Michael Badzioch, D. Timothy Bishop, Chris Evans, Steve Edwards, Julia Meitz, Sarah Bullock, Questa Hope, Michelle Guy, The ACTANE Consortium
Affiliations: Institute of Cancer Research and Royal Marsden National Health Service Trust Foundation Hospital, Sutton, UK (R.A.E., S.E., J.M., S.B., Q.H., and M.G.); Cancer Research U.K. Genetic Epidemiology Unit, Strangeways Research Labs, Cambridge, UK (D.F.E. and C.E.); Program in Cancer Genetics, Departments of Oncology and Human Genetics, McGill University, Montreal, Canada (W.D.F.); Cancer Genomics Laboratory, Centre hospitalier de l'Universite Laval Research Centre, Sainte-Foy, QC, Canada (J. Simard); Cancer Epidemiology Centre, Cancer Council Victoria (G.G.G.), and Centre for Genetic Epidemiology, University of Melbourne, Carlton, Australia (J.L.H.); Unit of Medical Genetics, Norwegian Radium Hospital, Oslo, Norway (L.M. and P.M.); Cancer Research U.K. Genetic Epidemiology Laboratory, St. James' University Hospital, Leeds, UK (T.B.); MD Anderson Cancer Center, Houston, TX, USA (M.B)

BC/CA/HI
Authors: Chih-lin Hsieh, Jerry Halpern, Raymond R. Balise, Ingrid Oakley-Girvan, Alice S. Whittemore
Affiliations: University of Southern California, Los Angeles, USA (C.-l.H.); Stanford University School of Medicine, Stanford, USA (J.H., R.N.B., and A.S.W.); Northern California Cancer Center, Union City and Stanford, USA (I.O.-G.)

Data Coordinating Center
Authors: Jianfeng Xu, Latchezar Dimitrov, Bao-Li Chang, Tamara S. Adams, Aubrey R. Turner, Deborah A. Meyers
Affiliations: Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, NC, USA (J.X., L.D., B.-L.C., T.S.A., A.R.T., and D.A.M.)

Fred Hutchinson Cancer Research Center/Institute for Systems Biology
Authors: Danielle M. Friedrichsen, Kerry Deutsch, Suzanne - Kolb, Marta Janer, Leroy Hood, Elaine A. Ostrander, Janet L. Stanford
Affiliations: Divisions of Human Biology (D.M.F.) and Public Health Sciences (S.K. and J.L.S.), Fred Hutchinson Cancer Center, and Institute for Systems Biology (K.D., M.J., and L.H.), Seattle, USA

Johns Hopkins University
Authors: Charles M. Ewing, Marta Gielzak, Sarah D. Isaacs, Patrick C. Walsh, Kathleen E. Wiley, William B. Isaacs
Affiliations: Department of Urology, Johns Hopkins Medical Institutions (C.M.E., M.G., S.D.I. P.C.W., K.E.W., and W.B.I), and Inherited Disease Research Branch, National Human Genome Research Institute, NIH (J.B.-W.), Baltimore, USA

University of Michigan
Authors: Ethan M. Lange, Lindsey A. Ho, Jennifer L. Beebe-Dimmer, David P. Wood, Kathleen A. Cooney
Affiliations: Departments of Genetics and Biostatistics, University of North Carolina, Chapel Hill, USA (E.M.L. and L.A.H); Departments of Internal Medicine and Urology, University of Michigan, Ann Arbor, USA (J.L.B.-D., D.P.W, and K.A.C.)

National Institutes of Health
Authors: Daniela Seminara
Affiliations: Cancer Genetics Branch, National Human Genome Research Institute, (E.A.O.), National Cancer Institute (NCI) (D.S.), and Inherited Disease Research Branch, National Human Genome Research Institute, (J.B-W.), National Institutes of Health, Bethesda, USA

University of Tampere and Tampere University Hospital
Authors: Tarja Ikonen, Agnes Baffoe-Bonnie, Henna Fredriksson, Mika P. Matikainen, Teuvo LJ Tammela, Joan Bailey-Wilson, Johanna Schleutker
Affiliations: University of Tampere and Tampere University Hospital, Tampere, Finland (T.I., H.F., M.P.M. T.L.T., and J. Schleutker); Fox Chase Cancer Center, Division of Population Science, Philadelphia, USA (A.B.-B.)

University of Ulm
Authors: Christiane Maier, Kathleen Herkommer, Josef J. Hoegel, Walther Vogel, Thomas Paiss
Affiliations: Abteilung Humangenetik, Universität Ulm, Ulm, Germany (C.M., J.J.H., and W.V.), and Urologische Universitätsklinik und Poliklinik, Abteilung für Urologie und Kinderurologie (K.H. and T.P.), Ulm, Germany

University of Umeå
Authors: Fredrik Wiklund, Monica Emanuelsson, Elisabeth Stenman, Björn-Anders Jonsson, Henrik Grönberg
Affiliations: Department of Radiation Sciences, Oncology, University of Umeå, Umeå, Sweden (F.W., M.E., E.S., B.-A.J., and H.G.)

University of Utah
Authors: Nicola J. Camp, James Farnham, Lisa A. Cannon-Albright
Affiliations: Division of Genetic Epidemiology, Department of Biomedical Informatics, University of Utah, Salt Lake City, USA (N.J.C., J.F., and L.C.A)

Washington University
Authors: William J. Catalona, Brian K. Suarez, and Kimberly A. Roehl
Affiliations: Department of Urology and the Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (W.J.C.); Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA (B.K.S and K.A.R.)

References

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 57:289–300

Berry R, Schroeder J, French A, McDonnell S, Peterson B, Cunningham J, Thibodeau S, Schaid D (2000) Evidence for a prostate cancer-susceptibility locus on chromosome 20. Am J Hum Genet 67:82–91

Berthon P, Valeri A, Cohen-Akenine A, Drelon E, Paiss T, Wohr G, Latil A, Millasseau P, Mellah I, Cohen N, Blanche H, Bellane-Chantelot C, Demenais F, Teillac P, Le Duc A, de Petriconi R, Hautmann R, Chumakov I, Bachner L, Maitland NJ, Lindereeau R, Vogel W, Fournier G, Mangin P, Cussenot O (1998) Predisposing gene for early-onset prostate cancer, localized on chromosome 1q42.2–43. Am J Hum Genet 62:1416–1424

Camp NJ, Farnham JM, Cannon-Albright LA (2005) Genomic search for prostate cancer predisposition loci in Utah pedigrees. Prostate 65:365–374

Carpten J, Nupponen N, Isaacs S, Sood R, Robbins C, Xu J, Faruque M, et al (2002) Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. Nat Genet 30:181–184

Carter B, Bova G, Beaty T, Steinberg G, Childs B, Isaacs W, Walsh P (1993) Hereditary prostate cancer: epidemiologic and clinical features. J Urol 150:797–802

Chang BL, Isaacs SD, Wiley KE, Gillanders EM, Zheng SL, Meyers DA, Walsh PC, Trent JM, Xu J, Isaacs WB (2005) Genome-wide screen for prostate cancer susceptibility genes in men with clinically significant disease. Prostate 64:356–361

Cunningham JM, McDonnell SK, Marks A, Hebbring S, Anderson SA, Peterson BJ, Slager S, French A, Blute ML, Schaid DJ, Thibodeau SN (2003) Genome linkage screen for prostate cancer susceptibility loci: results from the Mayo Clinic Familial Prostate Cancer Study. Prostate 57:335–346

Easton DF, Schaid DJ, Whittemore AS, Isaacs WJ (2003) Where are the prostate cancer genes?—A summary of eight genome wide searches. Prostate 57:261–269

Edwards S, Meitz J, Eeles R, Evans C, Easton D, Hopper J, Giles G, Foulkes WD, Narod S, Simard J, Badzioch M, Mahle L (2003) Results of a genome-wide linkage analysis in prostate cancer families ascertained through the ACTANE consortium. Prostate 57:270–279

Etzioni R, Penson DF, Legler JM, di Tommaso D, Boer R, Gann PH, Feuer EJ (2002) Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst 94:981–990

Feingold E, Brown PO, Siegmund D (1993) Gaussian models for genetic linkage analysis using complete high-resolution maps of identity by descent. Am J Hum Genet 53:234–251

Gibbs M, Stanford JL, McIndoe RA, Jarvik GP, Kolb S, Goode EL, Chakrabarti L, Schuster EF, Buckley VA, Miller EL, Brandzel S, Li S, Hood L, Ostrander EA (1999) Evidence for a rare prostate cancer-susceptibility locus at chromosome 1p36. Am J Hum Genet 64:776–787

Gillanders EM, Xu J, Chang BL, Lange EM, Wiklund F, Bailey-Wilson JE, Baffoe-Bonnie A, et al (2004) Combined genome-wide scan for prostate cancer susceptibility genes. J Natl Cancer Inst 96:1240–1247

Goddard KA, Witte JS, Suarez BK, Catalona WJ, Olson JM (2001) Model-free linkage analysis with covariates confirms linkage of prostate cancer to chromosomes 1 and 4. Am J Hum Genet 68:1197–1206

Grönberg H (2003) Prostate cancer epidemiology. Lancet 361:859–864

Hsieh C-L, Oakley-Girvan I, Balise RR, Halpern J, Gallagher RP, Wu AH, Kolonel LN, O'Brien LE, Lin IG, Van Den Berg DJ, Teh CZ, West DW, Whittemore AS (2001) A genome screen of families with multiple cases of prostate cancer: evidence of genetic heterogeneity. Am J Hum Genet 69:148–158

Janer M, Friedrichsen DM, Stanford JL, Badzioch MD, Kolb S, Deutsch K, Peters MA, Goode EL, Welti R, DeFrance HB, Iwasaki L, Li S, Hood L, Ostrander EA, Jarvik GP (2003) Genomic scan of 254 hereditary prostate cancer families. Prostate 57:309–319

Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ (2004) Cancer statistics, 2004. CA Cancer J Clin 54:8–29

Johns LE, Houlston RS (2003) A systematic review and meta-analysis of familial prostate cancer risk. BJU Int 91:789–794

Kong A, Cox NJ (1997) Allele-sharing models: LOD scores and accurate linkage tests. Am J Hum Genet 61:1179–1188

Kong A, Gudbjartsson D, Sainz J, Jonsdottir G, Gudjonsson S, Richardsson B, Sigurdardottir S, Barnard B, Hallbeck B, Masson M, Shlien A, Palsson S, Frigge M, Thorgeirsson T, Gulcher J, Stefansson K (2002) A high-resolution recombination map of the human genome. Nat Genet 31:241–247

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lander E, Kruglyak L (1995) Genetic dissection of complex traits: guidelines for interpreting and reporting results. Nature Genet 11:241–247

Lange EM, Gillanders EM, Davis CC, Brown WM, Campbell JK, Jones M, Gildea D, Riedesel E, Albertus J, Freas-Lutz D, Markey C, Giri V, Dimmer JB, Montie JE, Trent JM, Cooney KA (2003) Genome-wide scan for prostate cancer susceptibility genes using families from the University of Michigan prostate cancer genetics project finds evidence for linkage on chromosome 17 near BRCA1. Prostate 57:326–334

Lange EM, Ho LA, Beebe-Dimmer JL, Wang Y, Gillanders EM, Trent JM, Lange LA, Wood DP, Cooney KA (2006) Genome-wide linkage scan for prostate cancer susceptibility genes in men with aggressive disease: significant evidence for linkage at chromosome 15q12. Hum Genet 119:400–407

Lin DY (2005) An efficient Monte Carlo approach to assessing statistical significance in genomic studies. Bioinformatics 21:781–787

Lindor NM, Greene MH, Program tMFC (1998) The concise handbook of family cancer syndromes. J Natl Cancer Inst 14:1039–1071

Matsui H, Suzuki K, Ohtake N, Nakata S, Takeuchi T, Yamanaka H, Inoue I (2004) Genomewide linkage analysis of familial prostate cancer in the Japanese population. J Hum Genet 49:9–15

Nelson WG, De Marzo AM, DeWeese TL, Isaacs WB (2004) The role of inflammation in the pathogenesis of prostate cancer. J Urol 172:S6–S11; discussion S11–S12

Neville PJ, Conti DV, Paris PL, Levin H, Catalona WJ, Suarez BK, Witte JS, Casey G (2002) Prostate cancer aggressiveness locus on chromosome 7q32–q33 identified by linkage and allelic imbalance studies. Neoplasia 4:424–431

Neville PJ, Conti DV, Krumroy LM, Catalona WJ, Suarez BK, Witte JS, Casey G (2003) Prostate cancer aggressiveness locus on chromosome segment 19q12–q13.1 identified by linkage and allelic imbalance studies. Genes Chromosomes Cancer 36:332–339

Ostrander EA, Stanford JL (2000) Genetics of prostate cancer: too many loci, too few genes. Am J Hum Genet 67:1367–1375

Paiss T, Worner S, Kurtz F, Haeussler J, Hautmann RE, Gschwend JE, Herkommer K, Vogel W (2003) Linkage of aggressive prostate cancer to chromosome 7q31–33 in German prostate cancer families. Eur J Hum Genet 11:17–22

Schaid D (2004) The complex genetic epidemiology of prostate cancer. Hum Mol Genet 13(Review Issue):R103–R121

Schaid DJ, Chang BL (2005) Description of the International Consortium For Prostate Cancer Genetics, and failure to replicate linkage of hereditary prostate cancer to 20q13. Prostate 63:276–290

Schleutker J, Baffoe-Bonnie AB, Gillanders E, Kainu T, Jones MP, Freas-Lutz D, Markey C, Gildea D, Riedesel E, Albertus J, Gibbs KD Jr, Matikainen M, Koivisto PA, Tammela T, Bailey-Wilson JE, Trent JM, Kallioniemi OP (2003) Genome-wide scan for linkage in Finnish hereditary prostate cancer (HPC) families identifies novel susceptibility loci at 11q14 and 3p25–26. Prostate 57:280–289

Slager S, Schaid D, Cunningham J, McDonnell S, Marks A, Peterson B, Hebbring S, Anderson S, French A, Thibodeau S (2003) Confirmation of linkage of prostate cancer aggressiveness with chromosome 19q. Am J Hum Genet 72:759–762

Slager SL, Zarfas KE, Brown WM, Lange EM, McDonnell SK, Wojno KJ, Cooney KA (2006) Genome-wide linkage scan for prostate cancer aggressiveness loci using families from the University of Michigan Prostate Cancer Genetics Project. Prostate 66:173–179

Smith JR, Freije D, Carpten JD, Grönberg H, Xu J, Isaacs SD, Brownstein MJ, Bova GS, Guo H, Bujinovszky P, Nusskern DR, Damber JE, Bergh A, Emanuelsson M, Kallioniemi OP, Walker-Daniels J, Bailey-Wilson JE, Beaty TH, Meyers DA, Walsh PC, Collins FS, Trent JM, Isaacs WB (1996) Major susceptibility locus for prostate cancer on chromosome 1 suggested by a genome-wide search. Science 274:1371–1374

Stanford J, McDonnell S, Friedrichsen D, Carlson E, Kolb S, Deutsch K, Janer M, Hood L, Ostrander E, Schaid D (2006) Prostate cancer and genetic susceptibility: a genome scan incorporating disease aggressiveness. Prostate 66:317–325

Suarez BK, Lin J, Burmester JK, Broman KW, Weber JL, Banerjee TK, Goddard KAB, Witte JS, Elston RC, Catalona WJ (2000) A genome screen of multiplex prostate cancer sibships. Am J Hum Genet 66:933–944

Tavtigian S, Simard J, Teng D, Abtin V, Baumgard M, Beck A, Camp N, et al (2001) A strong candidate prostate cancer susceptibility gene at chromosome 17p. Nat Genet 27:172–180

Whittemore AS, Halpern J (2001) Problems in the definition, interpretation, and evaluation of genetic heterogeneity. Am J Hum Genet 68:457–465

Wiklund F, Gillanders EM, Albertus JA, Bergh A, Damber JE, Emanuelsson M, Freas-Lutz DL, Gildea DE, Goransson I, Jones MS, Jonsson BA, Lindmark F, Markey CJ, Riedesel EL, Stenman E, Trent JM, Grönberg H (2003) Genome-wide scan of Swedish families with hereditary prostate cancer: suggestive evidence of linkage at 5q11.2 and 19p13.3. Prostate 57:290–297

Witte J, Goddard K, Conti D, Elston R, Lin J, Suarez B, Broman K, Burmester J, Weber J, Catalona W (2000) Genomewide scan for prostate cancer-aggressiveness loci. Am J Hum Genet 67:92–99

Witte JS, Suarez BK, Thiel B, Lin J, Yu A, Banerjee TK, Burmester JK, Casey G, Catalona WJ (2003) Genome-wide scan of brothers: replication and fine mapping of prostate cancer susceptibility and aggressiveness loci. Prostate 57:298–308

Xu J (2000) Combined analysis of hereditary prostate cancer linkage to 1q24–25: results from 772 hereditary prostate cancer families from the International Consortium for Prostate Cancer Genetics. Am J Hum Genet 66:945–957

Xu J, Meyers D, Freije D, Isaacs S, Wiley K, Nusskern D, Ewing C, et al (1998) Evidence for a prostate cancer susceptibility locus on the X chromosome. Nat Genet 20:175–179

Xu J, Zheng SL, Hawkins GA, Faith DA, Kelly B, Isaacs SD, Wiley KE, Chang B, Ewing CM, Bujinovszky P, Carpten JD, Bleecker ER, Walsh PC, Trent JM, Meyers DA, Isaacs WB (2001) Linkage and association studies of prostate cancer susceptibility: evidence for linkage at 8p22–23. Am J Hum Genet 69:341–350

Xu J, Zheng SL, Komiya A, Mychaleckyj JC, Isaacs SD, Hu JJ, Sterling D, et al (2002) Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. Nat Genet 32:321–325

Xu J, Gillanders EM, Isaacs SD, Chang BL, Wiley KE, Zheng SL, Jones M, Gildea D, Riedesel E, Albertus J, Freas-Lutz D, Markey C, Meyers DA, Walsh PC, Trent JM, Isaacs WB (2003) Genome-wide scan for prostate cancer susceptibility genes in the Johns Hopkins hereditary prostate cancer families. Prostate 57:320–325

Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR, Meyers DA, Eeles RA, et al (2005) A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. Am J Hum Genet 77:219–229